COMMENTARY ➤ Daniel Morehead, MD
It’s Time for Us to Stop Waffling About Psychiatry
Imagine—or, better, remember—the following scenarios:

➤ You notice that a Harvard historian has published a book describing the history of psychiatry as a series of failures. This book receives praise from inside and outside psychiatry, garnering attention in major periodicals such as The Atlantic and The New Yorker.

➤ You see articles by prominent psychiatrists asserting that we should give up the idea that mental illness includes biological dysfunction, and either redefine mental illness or give up trying to define it altogether.

➤ You read articles by other prominent psychiatrists arguing that psychiatric treatment, including medications, should be decoupled from notions of biological dysfunction.

➤ You read an article by one of numerous psychiatrists and commentators who declare the field of psychiatry to be “in crisis,” and another discussing psychiatry’s particular vulnerability to “institutional corruption.”

TALES FROM THE CLINIC
My Life is Hell, Doc. Please Help Me!
➤ Sara Mournani, MD; Nidal Moukaddam, MD, PhD

In this installment of Tales From the Clinic: The Art of Psychiatry, we visit a case of severe anxiety in a young man who otherwise presents as the perfect patient who is treatment adherent. Individuals with anxiety suffer pervasive impairment in everyday life, and treatment is often not fully effective. Somatic and physical comorbidities typically complicate clinical anxiety presentation, but there are exciting conceptual and treatment considerations in this field worth highlighting, including novel concepts such as gut microbiome influence on anxiety disorders, high body awareness, and somatosensory amplification dimensions.

“Mr West,” aged 30 years, is a well-groomed, soft-spoken man who presents to the clinic for anxiety. He gives you access to extensive medical records spanning the past 8 years, during which time he has received treatment for generalized anxiety. He complains of intense anxiety, fatigue, and hopelessness on a daily basis. According to his records, he has received various medications for anxiety, but they have not been effective.

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Nery A. Diaz, DO, FAPA; Laura Clarke, MD, DFAPA; and Claire Holderness, MD

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Amanda Calhoun, MD, MPH

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See why it’s **THE #1 PRESCRIBED**
long-acting injectable atypical antipsychotic for adults with schizophrenia†

**INDICATION**

INVEGA SUSTENNA® (paliperidone palmitate) is indicated for the treatment of:
- Schizophrenia in adults.
- Schizoaffective disorder as monotherapy and as an adjunct to mood stabilizers or antidepressants in adults.

**IMPORTANT SAFETY INFORMATION FOR INVEGA SUSTENNA® (paliperidone palmitate)**

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

See full prescribing information for complete Boxed Warning.

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. INVEGA SUSTENNA® is not approved for use in patients with dementia-related psychosis.

Please see additional Important Safety Information and Brief Summary of the full Prescribing Information for INVEGA SUSTENNA® on following pages of this advertisement.

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**Consider once-monthly INVEGA SUSTENNA® for your adult patients with schizophrenia...**

INVEGA SUSTENNA® has clinical evidence compared to a group of oral antipsychotics for adults recently diagnosed with schizophrenia within 1 to 5 years†‡

INVEGA SUSTENNA® was evaluated in 4 short-term, double-blind, randomized, placebo-controlled pivotal trials and 1 longer-term, double-blind, placebo-controlled pivotal trial³

INVEGA SUSTENNA® was compared to a group of commonly prescribed oral antipsychotics in a study with a real world design†‡

**...and for your adult patients with schizoaffective disorder**

INVEGA SUSTENNA® was evaluated in a long-term schizoaffective disorder study vs placebo both as a monotherapy and as an adjunctive therapy³§

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*These data have not been verified for patients with schizoaffective disorder.
†All patients were diagnosed 1 to 5 years previously with ≥2 relapses requiring hospitalization.
‡The study was not powered to compare the efficacy of INVEGA SUSTENNA® with that of individual oral antipsychotics.
§Adjunct to antidepressants or mood stabilizers. 39 mg strength was not studied in the long-term schizoaffective disorder study.
¶Real world as defined by patient selection and clinically meaningful outcome measures.

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Scan to view safety and efficacy data for adults with schizophrenia or visit InvegaSustennaHCP.com

Scan to view safety and efficacy data for adults with schizoaffective disorder or visit InvegaSustennaHCP.com/efficacy-schizoaffective
IMPORTANT SAFETY INFORMATION (cont’d)

Contraindications: INVEGA SUSTENNA® is contraindicated in patients with a known hypersensitivity to either paliperidone, risperidone, or to any excipients of the INVEGA SUSTENNA® formulation.

Cerebrovascular Adverse Reactions: Cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack), including fatalities, were reported at a higher incidence in elderly patients with dementia-related psychosis taking risperidone, aripiprazole, and olanzapine compared to placebo. No studies have been conducted with oral paliperidone, INVEGA SUSTENNA®, or the 3-month paliperidone palmitate extended-release injectable suspension in elderly patients with dementia. These medicines are not approved for the treatment of patients with dementia-related psychosis.

Neuroleptic Malignant Syndrome (NMS): NMS, a potentially fatal symptom complex, has been reported in association with antipsychotic drugs, including paliperidone. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status including delirium, and autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (Habomylpolysis), and acute renal failure.

If NMS is suspected, immediately discontinue INVEGA SUSTENNA® and provide symptomatic treatment and monitoring.

QT Prolongation: Paliperidone causes a modest increase in the corrected QT (QTc) interval. Avoid the use of drugs that also increase QTc interval and in patients with risk factors for prolonged QTc interval. Paliperidone should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias. Certain circumstances may increase the risk of the occurrence of torsades de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval.

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

The risk of developing TD and the likelihood that it will become irreversible appear to increase with the duration of treatment and the cumulative dose. The syndrome can develop after relatively brief treatment periods, even at low doses. It may also occur after discontinuation. TD may remit, partially or completely, if antipsychotic treatment is discontinued. Antipsychotic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome, possibly masking the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

If signs and symptoms of TD appear in a patient on INVEGA SUSTENNA®, drug discontinuation should be considered. However, some patients may require treatment with INVEGA SUSTENNA® despite the presence of the syndrome. In patients who do require chronic treatment, use the lowest dose and the shortest duration of treatment producing a satisfactory clinical response. Periodically reassess the need for continued treatment.

Metabolic Changes: Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and body weight gain. While 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 and diabetes mellitus, in some cases extreme and associated with ketoadipic acid, hyperosmolar coma or death, have been reported in patients treated with all atypical antipsychotics (APS). Patients starting treatment with APS who have or are at risk for diabetes mellitus should undergo fasting blood glucose testing at the beginning of and during treatment. Patients who develop symptoms of hyperglycemia during treatment should also undergo fasting blood glucose testing. All patients treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia. Some patients require continuation of antidiabetic treatment despite discontinuation of the suspect drug.

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

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

Orthostatic Hypotension and Syncope: INVEGA SUSTENNA® may induce orthostatic hypotension in some patients due to its alpha-adrenergic blocking activity. INVEGA SUSTENNA® should be used with caution in patients with known cardiovascular disease, cerebrovascular disease or conditions that would predispose patients to hypotension (e.g., dehydratation, hypovolemia, treatment with antihypertensive medications). Monitoring should be considered in patients for whom this may be of concern.

Falls: Somnolence, postural hypotension, motor and sensory instability have been reported with the use of antipsychotics, including INVEGA SUSTENNA®, which may lead to falls and, consequently, fractures or other fall-related injuries. For patients, particularly the elderly, with diseases, conditions, or medications that could exacerbate these effects, assess the risk of falls when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

Leukopenia, Neutropenia and Agranulocytosis have been reported with antipsychotics, including INVEGA SUSTENNA®. In patients with a history of clinically significant low white blood cell count (WBC)/absolute neutrophil count (ANC) or drug-induced leukopenia/neutropenia, perform a complete blood count frequently during the first few months of therapy. Consider discontinuing INVEGA SUSTENNA® at the first sign of a clinically significant decline in WBC in the absence of other causative factors. Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treat promptly if such symptoms or signs occur.

Discontinue INVEGA SUSTENNA® in patients with severe neutropenia (absolute neutrophil count <1000/mm3) and follow their WBC until recovery.

Hyperprolactinemia: As with other drugs that antagonize dopamine D2 receptors, INVEGA SUSTENNA® elevates prolactin, which can lead to increased incidence of galactorrhea, galactorrhea, and amenorrhea. Although the prevalence of the syndrome appears to be associated with higher levels of prolactin elevation than other antipsychotic agents.

Potential for Cognitive and Motor Impairment: Somnolence, sedation, and dizziness were reported as adverse reactions in subjects treated with INVEGA SUSTENNA®. INVEGA SUSTENNA® has the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about performing activities that require mental alertness such as operating hazardous machinery, including motor vehicles, until they are reasonably certain that INVEGA SUSTENNA® does not adversely affect them.

Seizures: INVEGA SUSTENNA® should be used cautiously in patients with a history of seizures or with conditions that potentially lower seizure threshold. Conditions that lower seizure threshold may be more prevalent in patients 65 years or older.

Administration: For intramuscular injection only by a healthcare professional using only the needles provided in the INVEGA SUSTENNA® kit. Care should be taken to avoid inadvertent injection into a blood vessel.

Drug Interactions: Strong CYP3A4/P-glycoprotein (P-gp) inducers: Avoid using a strong inducer of CYP3A4 and/or P-gp (e.g. carbamazepine, rifampin, St. John’s Wort) during a dosage interval for INVEGA SUSTENNA®. If administering a strong inducer is necessary, consider managing the patient using paliperidone extended-release tablets.

Pregnancy/Nursing: INVEGA SUSTENNA® may cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. Advise patients to notify their pregnancy registry that monitors outcomes in women exposed to INVEGA SUSTENNA® during pregnancy. INVEGA SUSTENNA® can pass into human breast milk. The benefits of breastfeeding should be considered along with the mother’s clinical need for INVEGA SUSTENNA® and any potential adverse effects on the breastfed infant from INVEGA SUSTENNA® or the mother’s underlying condition.

Commonly Observed Adverse Reactions for INVEGA SUSTENNA®: The most common adverse reactions in clinical trials in patients with schizophrenia (25% and twice placebo) were injection site reactions, somnolence/sedation, dizziness, akathisia and extrapyramidal disorder. No adverse events occurred at a rate of 5% and twice placebo during the 15-month double-blind, placebo-controlled study in patients with schizoaffective disorder. The following adverse reactions occurred more frequently (a ≥2% difference vs. placebo) in the long-term study in patients with schizoaffective disorder: weight increased, nasopharyngitis, headache, hyperprolactinemia, and pyrexia.

Before prescribing INVEGA SUSTENNA®, please review the full Prescribing Information, including Boxed WARNING, available at www.InvegaSustennahcp.com. Please see Brief Summary of full Prescribing Information on following pages of this advertisement.

**INDICATIONS AND USAGE**

**INVEGA SUSTENNA®** (paliperidone palmitate) is indicated for the treatment of:

- Schizophrenia in adult patients (see Clinical Studies (14.1) in Full Prescribing Information).

- Schizoaffective disorder in adults as monotherapy and as an adjunct to mood stabilizers or antidepressants (see Clinical Studies (14.2) in Full Prescribing Information).

**CONTRAINDICATIONS**

**INVEGA SUSTENNA®** is contraindicated in patients with a known hypersensitivity to either paliperidone or paliperidone palmitate, or to any of the excipients in the INVEGA SUSTENNA® formulation.

**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 compared to placebo. Studies show that the use of antipsychotics in older patients with dementia may cause increased mortality. Patients with dementia-related psychosis treated with antipsychotics should be monitored regularly for worsening of conditions that could be expected with age, or with dementia. Tragic cases of suicide or unexpected death have been reported in elderly and/or demented patients treated with antipsychotics, including those with dementia.

**Neuroleptic Malignant Syndrome (NMS)**

Neuroleptic Malignant Syndrome (NMS), a potentially fatal symptom complex, has been reported with antipsychotic therapy, including paliperidone. Dementia-related psychosis is a risk factor for NMS. The syndrome, which can develop after relatively brief treatment, may occur at low doses, and may be reversible if treatment is withdrawn. Although not all cases fit this description, signs include hyperpyrexia, muscle rigidity, altered mental status including delirium, and autonomic instability (hypertension or hypotension, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

If NMS is suspected, immediately discontinue INVEGA SUSTENNA® and provide symptomatic treatment and monitoring. Supportive treatment consists of managing signs of autonomic instability and controlling body temperature. If aNMS is suspected, immediately discontinue INVEGA SUSTENNA® and provide symptomatic treatment and monitoring. Supportive treatment consists of managing signs of autonomic instability and controlling body temperature.

**QT Prolongation**

Paliperidone causes a modest increase in the corrected QT (QTc) interval. The use of paliperidone should be avoided in combination with other drugs that are known to prolong QTc intervals due to Class IA (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic medications, antipsychotic medications (e.g., chlorpromazine, thioridazine), antibiotics (e.g., gentamicin, moxifloxacin), or any other class of medications known to prolong the QTc interval. Paliperidone should also be avoided in patients with congenital QT prolongation, including long QT syndrome and in patients with a history of cardiac arrhythmias.

Certain circumstances may increase the risk of the occurrence of Torsades de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including (1) hypokalemia, (2) hypomagnesemia, (3) hypoxia, (4) use of other drugs that prolong the QTc interval; and (5) presence of congenital prolongation of the QT interval. The effects of oral paliperidone on the QT interval were evaluated in a double-blind, active-controlled, multicenter QT study in adults with schizophrenia and schizoaffective disorder, and in a long-term open-label pharmacokinetic and safety study in subjects with schizophrenia in which the highest dose of paliperidone (9 mg/day) was evaluated.

In the QT study (n=141), the 8 mg dose of immediate-release oral paliperidone (n=50) showed a mean placebo-subtracted QTcLD of 6.8 msec (90% CI: 3.6; 10.1) on day 2 at 1.5 hours post-dose. In the three fixed-dose efficacy studies of oral paliperidone extended release in subjects with schizophrenia, showed an increased placebo-subtracted QTcLD of 6.8 msec (90% CI: 3.6; 10.1) on day 2 at 1.5 hours post-dose.

Subjects with Schizophrenia

Pooled data from the four placebo-controlled (one 9-week and three 13-week), fixed-dose studies in subjects with schizophrenia are presented in Table 1.

<table>
<thead>
<tr>
<th>Placebo</th>
<th>39 mg</th>
<th>78 mg</th>
<th>156 mg</th>
<th>234/35 mg</th>
<th>234/156 mg</th>
<th>234/234 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change from baseline (mg/dL)</td>
<td>n=198</td>
<td>n=366</td>
<td>n=366</td>
<td>n=366</td>
<td>n=366</td>
<td>n=366</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>n=396</td>
<td>n=396</td>
<td>n=396</td>
<td>n=396</td>
<td>n=396</td>
<td>n=396</td>
</tr>
<tr>
<td>LDL</td>
<td>n=275</td>
<td>n=275</td>
<td>n=275</td>
<td>n=275</td>
<td>n=275</td>
<td>n=275</td>
</tr>
<tr>
<td>HDL</td>
<td>n=286</td>
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<td>n=286</td>
<td>n=286</td>
<td>n=286</td>
<td>n=286</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>n=387</td>
<td>n=387</td>
<td>n=387</td>
<td>n=387</td>
<td>n=387</td>
<td>n=387</td>
</tr>
</tbody>
</table>

**Metabolic Changes**

Hyperglycemia and diabetes mellitus, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, have been reported in patients treated with all atypical antipsychotics. These changes have occurred in patients for whom alternative, non-pharmacological interventions were not effective. In the three fixed-dose efficacy studies, no subject experienced a change in QTcLD exceeding 12 (moderate), 20 (severe), or 30 (high) milliseconds.

**Hyperglycemia**

Hyperglycemia and diabetes mellitus, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, have been reported in patients treated with all atypical antipsychotics. These changes have occurred in patients for whom alternative, non-pharmacological interventions were not effective. In the three fixed-dose efficacy studies, no subject experienced a change in QTcLD exceeding 12 (moderate), 20 (severe), or 30 (high) milliseconds.

**Diabetes**

In a long-term open-label pharmacokinetic and safety study in subjects with schizophrenia in which the highest dose of paliperidone (9 mg/day) was evaluated, INVEGA SUSTENNA® was associated with a mean change in glucose of -0.4 mg/dL at Week 29 (n=109) and +6.8 mg/dL at Week 53 (n=113).

During the initial 25-week open-label period of a long-term study in subjects with schizophrenia, changes in mean glucose with paliperidone were from baseline: -0.3 mg/dL at Week 1 (n=109) and +13.2 mg/dL at Week 13 (n=109).

In the three fixed-dose efficacy studies, no subject experienced a change in QTcLD exceeding 12 (moderate), 20 (severe), or 30 (high) milliseconds.

**Table 1: Change in Fasting Glucose from Four Placebo-Controlled, 9- to 13-Week, Fixed-Dose Studies in Subjects with Schizophrenia**

<table>
<thead>
<tr>
<th>Placebo</th>
<th>39 mg</th>
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Hyperglycemia and diabetes mellitus, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, have been reported in patients treated with all atypical antipsychotics. These changes have occurred in patients for whom alternative, non-pharmacological interventions were not effective. In the three fixed-dose efficacy studies, no subject experienced a change in QTcLD exceeding 12 (moderate), 20 (severe), or 30 (high) milliseconds.

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During the initial 25-week open-label period of a long-term study in subjects with schizophrenia, changes in mean glucose with paliperidone were from baseline: -0.3 mg/dL at Week 1 (n=109) and +13.2 mg/dL at Week 13 (n=109).

In the three fixed-dose efficacy studies, no subject experienced a change in QTcLD exceeding 12 (moderate), 20 (severe), or 30 (high) milliseconds.
INVEGA SUSTENNA® (paliperidone palmitate) extended-release injectable suspension, for intramuscular use

In a long-term open-label pharmacokinetic and safety study in subjects with schizophrenia in which the highest dose (39 mg) was evaluated, the mean change from baseline in lipids are presented in Table 3. The mean change from baseline in lipids during the initial 35-week open-label period and at the endpoint of the subsequent 15-month double-blind period in a long-term study in subjects with schizoaffective disorder are presented in Table 4.

The mean change from baseline in lipids during the initial 35-week open-label period and at the endpoint of the subsequent 15-month double-blind period in a long-term study in subjects with schizoaffective disorder are presented in Table 5.

### Table 3: Change in Fasting Lipids from an Open-Label and Double-Blind Periods of a Long-Term Study in Subjects with Schizophrenia

| Table 3: Change in Fasting Lipids from an Open-Label and Double-Blind Periods of a Long-Term Study in Subjects with Schizophrenia |
|------------------|------------------|------------------|

### Table 4: Change in Mean Weight from Baseline in Subjects with Schizoaffective Disorder

| Table 4: Change in Mean Weight from Baseline in Subjects with Schizoaffective Disorder |
|------------------|------------------|

### Table 5: Mean Change in Body Weight and the Proportion of Subjects with ≥ 7% Gain in Body Weight from Four Placebo-Controlled, 9- to 13-Week, Fixed-Dose Studies in Subjects with Schizophrenia

| Table 5: Mean Change in Body Weight and the Proportion of Subjects with ≥ 7% Gain in Body Weight from Four Placebo-Controlled, 9- to 13-Week, Fixed-Dose Studies in Subjects with Schizophrenia |
|------------------|------------------|------------------|------------------|------------------|

Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treat promptly if such symptoms or signs occur. INVEGA SUSTENNA® in patients with severe neutropenia (absolute neutrophil count < 10,000/mm³) and follow their WBC until recovery.

### Hyperprolactinemia

Like all antipsychotics, INVEGA SUSTENNA® elevates prolactin levels and the elevation persists during chronic administration. Paliperidone has a prolactin-elevating effect similar to that seen with reboxetine, a drug that is associated with a higher risk of prolactin elevation than antipsychotics.

### Anticholinergic Effects

Anticholinergic effects of INVEGA SUSTENNA®, regardless of etiology, may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotrophin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in premenopausal women and men, but data are not available for postmenopausal women. Gynaecomastia has been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypothalamic-gonadotrophin dysfunction may be reasonably certain that paliperidone therapy does not adversely affect them.

### Potential for Cognitive and Motor Impairment

Dysfunction of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents.

### Dysphagia

Drugs with alpha-adrenergic blocking effects have been reported as adverse reactions in subjects treated with INVEGA SUSTENNA®. Praag has been reported with oral paliperdone during postmarketing surveillance. Severe priapism may require surgical intervention.

### Dissociation of Body Temperature Regulation

Paliperidone can induce orthostatic hypotension and syncope in some patients because of its alpha-adrenergic blocking activity. Syncope was reported in < 1% (4/129) of subjects treated with INVEGA SUSTENNA® in the recommended dose range of 39 mg to 234 mg in four the fixed-dose, double-blind, placebo-controlled trials compared with 5% (5/115) of subjects treated with placebo. In the fixed-dose efficacy studies in subjects with schizophrenia, orthostatic hypotension was reported as an adverse event by < 1% (2/1290) of subjects treated compared to 0% (0/115) with placebo. Incidences of orthostatic hypotension and syncope in the long-term studies in subjects with schizophrenia and schizoaffective disorder were similar to those observed in the short-term studies.

### Inhibition of alpha-adrenergic Receptors

Orthostatic hypotension and syncope

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Paliperidone can induce orthostatic hypotension and syncope in some patients because of its alpha-adrenergic blocking activity. Syncope was reported in < 1% (4/129) of subjects treated with INVEGA SUSTENNA®. Praag has been reported with oral paliperdone during postmarketing surveillance. Severe priapism may require surgical intervention.
in previous double-blind, placebo-controlled clinical trials in adult subjects with schizophrenia. The safety of INVEGA SUSTENNA® in four fixed-dose, double-blind, placebo-controlled trials (nine 9-week and three 13-week studies), 849 received INVEGA SUSTENNA® in the maintenance trial (median exposure 229 days during the initial 35-week open-label phase of this study, of whom 295 continued to receive INVEGA SUSTENNA® during the double-blind placebo-controlled phase of this study (median exposure 171 days), and 875 received INVEGA SUSTENNA® in five non-placebo-controlled trials (three noninferiority active-comparator, trials, one long-term open-label pharmacokinetic and safety study, and an injection site [deltoid-gluteal] cross-over trial). One of the 13-week studies included a 234 mg INVEGA SUSTENNA® initiation dose followed by treatment with either 39 mg, 156 mg, or 234 mg every 4 weeks.

The safety of INVEGA SUSTENNA® was also evaluated in a 15-month, long-term study comparing INVEGA SUSTENNA® to selected oral antipsychotic therapies in adult subjects with schizophrenia. A total of 226 subjects received INVEGA SUSTENNA® during the 15-month, open-label period of this study, 218 subjects received selected oral antipsychotic therapies. The safety of INVEGA SUSTENNA® was similar to that seen in previous double-blind, placebo-controlled clinical trials in adult subjects with schizophrenia. The safety of INVEGA SUSTENNA® was also evaluated in a long-term study in adult subjects with schizoaffective disorder. A total of 987 subjects received INVEGA SUSTENNA® during the initial 25-week open-label period of this study (median exposure 167 days), 184 subjects continued to receive INVEGA SUSTENNA® during the 15-month blinded placebo-controlled period of this study (median exposure 446 days). Adverse reactions that occurred more frequently in INVEGA SUSTENNA® than the placebo group (a 2% difference or more between groups) were weight increased, nasopharyngitis, headache, hyperprolactinemia, and pyrexia.

Adverse Reactions in Double-Blind, Placeto-Controlled Clinical Trials

Commonly Observed Adverse Reactions: The most common (at least 5%) in any INVEGA SUSTENNA® group and likely drug-related (adverse events for which the drug rate is at least twice the placebo rate) adverse reactions from the double-blind, placebo-controlled trials in subjects with schizophrenia were injection site reactions, somnolence/sedation, dizziness, akathisia, and extrapyramidal disorder. No occurrences of adverse events reached this threshold in the long-term double-blind, placebo-controlled study in subjects with schizoaffective disorder.

Discontinuation of Treatment Due to Adverse Events: The percentage of subjects who discontinued due to adverse events in the four fixed-dose, double-blind, placebo-controlled schizophrenia trials were similar for INVEGA SUSTENNA® and placebo-treated subjects.

The percentage of subjects who discontinued due to adverse events in the open-label period of the long-term study in subjects with schizoaffective disorder was 7.5%. During the double-blind, placebo-controlled period of that study, the percentages of subjects who discontinued due to adverse events were 5.5% and 1.8% in INVEGA SUSTENNA®- and placebo-treated subjects, respectively.

Dose-Related Adverse Reactions: Based on the pooled data from the four fixed-dose, double-blind, placebo-controlled studies in adults with schizophrenia, among adverse reactions that occurred with 2% incidence in the subjects treated with INVEGA SUSTENNA®, only akathisia increased with dose. Hyperprolactinemia also exhibited a dose relationship, but did not occur at ≥ 1% incidence in INVEGA SUSTENNA®-treated subjects from the four fixed-dose studies.

Adverse Reactions Occurring at an Incidence of 2% or More in INVEGA SUSTENNA®-Treated Patients: Table 6 shows the adverse reactions reported in 2% or more of INVEGA SUSTENNA®-treated subjects and at a greater proportion than in the placebo group with schizophrenia in the four fixed-dose, double-blind, placebo-controlled trials.

Table 6: Incidences of Adverse Reactions 2% or More of INVEGA SUSTENNA®-Treated Patients (and Greater than Placebo) with Schizophrenia in Four Fixed-Dose, Double-Blind, Placebo-Controlled Trials

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>INVEGA SUSTENNA®</th>
<th>Placebob</th>
<th>39 mg (N=150)</th>
<th>78 mg (N=302)</th>
<th>156 mg (N=121)</th>
<th>234 mg/39 mg (N=165)</th>
<th>234 mg/78 mg (N=156)</th>
<th>234 mg/156 mg (N=165)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal stiffness</td>
<td>1</td>
<td>1</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain intensity</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Percentages are rounded to whole numbers. Table includes adverse reactions that were reported in 2% or more of subjects in any of the INVEGA SUSTENNA® dose groups and which occurred at greater incidence than in the placebo group.

1 Placebo group is pooled from all studies and included only delirium or gluteal injection during study period.

2 Initial delirium injection of 234 mg followed by either 39 mg, 156 mg, or 234 mg every 4 weeks by deltoid or gluteal injection. Other dose groups (39 mg, 78 mg, and 156 mg) are from studies involving only gluteal injection. (See Clinical Studies (14.3) in Full Prescribing Information).

Adverse reactions for which the INVEGA SUSTENNA® incidence was equal to or less than placebo are not listed in the table, but included the following: dyspnea, psychotic disorder, schizophrenia, and tremor. The following terms were combined: somnolence/sedation, breast tenderness/breast pain, abdominal discomfort/abdominal pain, upper/mastoid/abdominal discomfort, tachycardias/sinus tachycardia/heart rate increased. All injection site reaction-related adverse reactions were collapsed and are grouped under “Injection site reactions.”

Other Adverse Reactions Observed During the Clinical Trial Evaluation of INVEGA SUSTENNA®

The following list does not include reactions: 1) already listed in previous tables or elsewhere in labeling, 2) which were so general as to be uninformative, or 4) which were not considered to have significant clinical implications.

Cardiac disorders: atrioventricular block first degree, bradycardia, bundle branch block, palpitations, postural orthostatic tachycardia syndrome, tachycardia

Ear and labyrinth disorders: vertigo

Eye disorders: eye movement disorder, eye retraction, ocular ecchymosis, eczema blisters

Gastrointestinal disorders: constipation, dysphagia, flatulence, salivary hyposecretion

Immune system disorders: hypersensitivity

Infections and infestations: exocrine amylase transferase increased, aspartate aminotransferase increased, electrocardiogram abnormal

Metabolism and nutrition disorders: decreased appetite, hyperlipidemia, increased appetite

Musculoskeletal and connective tissue disorders: arthralgia, joint stiffness, muscle rigidity, muscle spasm, muscle tightness, muscle twitching, nuchal rigidity

Nervous system disorders: bradykinesia, cerebrovascular accident, cogan syndrome, convulsion, disorientation, dystonia, dyskinesia, dystonia, hypotonia, hypothermia, oromandibular dystonia, parkinsonism, psychomotor hyperactivity, syncope

Psychiatric disorders: insomnia, libido decreased, restlessness

Reproductive system and breast disorders: amenorrhea, breast discharge, breast enlargement/breast swelling, breast tenderness/breast pain, ejaculation disorder, erectile dysfunction, galactorrhea, gynecomastia, menstrual disorder, menstruation delayed, menstruation irregular, sexual dysfunction

Respiratory, thoracic and mediastinal disorders: nasal congestion

Skin and subcutaneous tissue disorders: drug eruption, pruritus, pruritus generalis, rash, urticaria

Demographic Differences

An examination of population subgroups in the double-blind placebo-controlled trials did not reveal any evidence of differences in safety on the basis of age, gender, or race alone; however, there were few subjects 65 years of age and older.

Extrapyramidal Symptoms (EPS)

Pooled data from the two double-blind, placebo-controlled, 13-week, fixed-dose trials in adult subjects with schizophrenia provided information regarding EPS. Several methods were used to measure EPS: (1) the Simpson-Angus global score which broadly evaluates parkinsonism, (2) the Barnes Akathisia Rating Scale which evaluates akathisia, and (4) use of anticholinergic medications to treat EPS (Table 7), and (5) incidence of spontaneous reports of EPS (Table 8).

<table>
<thead>
<tr>
<th>Simpson-Angus Global Score</th>
<th>INVEGA SUSTENNA®</th>
<th>Placeboa</th>
<th>39 mg (N=110)</th>
<th>78 mg (N=302)</th>
<th>156 mg (N=121)</th>
<th>234 mg/39 mg (N=165)</th>
<th>234 mg/78 mg (N=156)</th>
<th>234 mg/156 mg (N=165)</th>
</tr>
</thead>
<tbody>
<tr>
<td>scale</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lack of psychomotor slowing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rigidity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Akathisiaa</td>
<td>5</td>
<td>5</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Dyskinesiaa</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Use of Anticholinergic Medicationsa</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>7</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>
and risperidone long-acting injection can be found in the postmarketing experience in patients who have previously tolerated oral risperidone or oral paliperidone. The following adverse reactions have been identified during postapproval use of paliperidone; because these

### Postmarketing Experience

#### Vascular disorders:
- Rash papular

#### Reproductive system and breast disorders:
- Sleep disorder

#### Nervous system disorders:
- Musculoskeletal pain, torticollis, trismus

#### Musculoskeletal and connective tissue disorders:

#### Infections and infestations:
- Bundle branch block left, sinus arrhythmia

The following is a list of additional adverse reactions that have been reported in clinical trials with oral paliperidone:

69–100% of subjects in both the INVEGA SUSTENNA® and placebo groups. At Day 92, investigators rated the injection site after the first injection for redness, swelling, induration, and pain were rated as absent for INVEGA SUSTENNA® treatment included hyperkinesia (12.3%), parkinsonism (8.7%), tremor (0.3%), dyskinesia (0.3%) and dystonia (0.2%). During the 15-month double-blind treatment, the incidence of any EPS was similar to that of the placebo group (8.3% and 7.1% respectively). The most commonly reported treatment-emergent EPS-related adverse events (≥ 2%) in any treatment group in the double-blind phase of the study INVEGA SUSTENNA® versus placebo were hyperkinesia (3.7% vs. 2.3%), parkinsonism (0.5% vs. 1.4%), and tremor (1.2% vs. 2.4%).

Dystonia

Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms may occur at low doses, greater severity may be seen at higher doses. Symptoms may also occur with lower doses in patients with marked motor restlessness. The symptoms are usually treated with anticholinergics or benzodiazepines and may be managed with repeated injections of botulinum toxin type A. These symptoms may be associated with spontaneous resolution after a period of days to weeks and, rarely, with only one occurrence. Of 517 subjects who received INVEGA SUSTENNA®, 156 mg, 78 mg, 234 mg, and 39 mg, the incidence of EPS was ≤ 1%. At all doses of INVEGA SUSTENNA®, the incidence of EPS was ≤ 1%.

INVEGA SUSTENNA® (paliperidone palmitate) extended-release injectable suspension, for intramuscular use

<table>
<thead>
<tr>
<th>Concomitant Drug Name</th>
<th>Concomitant Drug Class</th>
<th>Clinical Rationale</th>
<th>Clinical Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centrally Acting Drugs and Alcohol</td>
<td>Given the primary CNS effects of paliperidone, concomitant use of centrally acting drugs and alcohol may modulate the CNS effects of INVEGA SUSTENNA®</td>
<td>INVEGA SUSTENNA® should be used with caution in combination with other centrally acting drugs and alcohol [see Adverse Reactions].</td>
<td>Monitor orthostatic vital signs in patients who are vulnerable to hypotension [see Warnings and Precautions].</td>
</tr>
<tr>
<td>Drugs with Potential for Inducing Orthostatic Hypotension</td>
<td>Because INVEGA SUSTENNA® has the potential for inducing orthostatic hypotension, the concomitant use of drugs that may decrease the effects of paliperidone [see Clinical Pharmacology (12.3) in Full prescribing Information]</td>
<td>Avoid using CYP3A4 and/or P-gp inducers with INVEGA SUSTENNA® during the 1-month dosing interval, if possible. If administering a strong inducer is necessary, consider managing the patient using paliperidone extended-release tablets [see Dosage and Administration (2.9) in Full prescribing Information].</td>
<td>Monitor orthostatic vital signs in patients who are vulnerable to hypotension [see Warnings and Precautions].</td>
</tr>
<tr>
<td>Levodopa and Other Dopamine Agonists</td>
<td>Paliperidone may antagonize the effect of levodopa and other dopamine agonists</td>
<td>Monitor and manage patient as clinically appropriate.</td>
<td></td>
</tr>
</tbody>
</table>

**INVEGA SUSTENNA® (paliperidone palmitate) extended-release injectable suspension, for intramuscular use**

**Table 2: Extrapyramidal Symptoms (EPS)-Related Conditions**, *MedDRA Preferred Term—Schizophrenia Studies in Adults*

<table>
<thead>
<tr>
<th>EPS Group</th>
<th>Placebo (N=262)</th>
<th>23 mg (N=130)</th>
<th>39 mg (N=223)</th>
<th>78 mg (N=223)</th>
<th>156 mg (N=228)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall percentage of subjects with EPS-related adverse events</td>
<td>10</td>
<td>12</td>
<td>11</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>5</td>
<td>6</td>
<td>6</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Hyperkinesia</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Tremor</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Dyskinesia</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Dystonia</td>
<td>9</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

**Table 3: Clinically Important Drug Interactions with INVEGA SUSTENNA®**

**Table 4: Extrapyramidal Symptoms (EPS)-Related Conditions**

<table>
<thead>
<tr>
<th>Concomitant Drug Name</th>
<th>Concomitant Drug Class</th>
<th>Clinical Rationale</th>
<th>Clinical Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centrally Acting Drugs and Alcohol</td>
<td>Given the primary CNS effects of paliperidone, concomitant use of centrally acting drugs and alcohol may modulate the CNS effects of INVEGA SUSTENNA®</td>
<td>INVEGA SUSTENNA® should be used with caution in combination with other centrally acting drugs and alcohol [see Adverse Reactions].</td>
<td>Monitor orthostatic vital signs in patients who are vulnerable to hypotension [see Warnings and Precautions].</td>
</tr>
<tr>
<td>Drugs with Potential for Inducing Orthostatic Hypotension</td>
<td>Because INVEGA SUSTENNA® has the potential for inducing orthostatic hypotension, the concomitant use of drugs that may decrease the effects of paliperidone [see Clinical Pharmacology (12.3) in Full prescribing Information]</td>
<td>Avoid using CYP3A4 and/or P-gp inducers with INVEGA SUSTENNA® during the 1-month dosing interval, if possible. If administering a strong inducer is necessary, consider managing the patient using paliperidone extended-release tablets [see Dosage and Administration (2.9) in Full prescribing Information].</td>
<td>Monitor orthostatic vital signs in patients who are vulnerable to hypotension [see Warnings and Precautions].</td>
</tr>
<tr>
<td>Levodopa and Other Dopamine Agonists</td>
<td>Paliperidone may antagonize the effect of levodopa and other dopamine agonists</td>
<td>Monitor and manage patient as clinically appropriate.</td>
<td></td>
</tr>
</tbody>
</table>

**INVEGA SUSTENNA® (paliperidone palmitate) extended-release injectable suspension, for intramuscular use**

**Table 5: Clinically Important Drug Interactions with INVEGA SUSTENNA®**

**Table 6: Extrapyramidal Symptoms (EPS)-Related Conditions**

<table>
<thead>
<tr>
<th>Concomitant Drug Name</th>
<th>Concomitant Drug Class</th>
<th>Clinical Rationale</th>
<th>Clinical Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centrally Acting Drugs and Alcohol</td>
<td>Given the primary CNS effects of paliperidone, concomitant use of centrally acting drugs and alcohol may modulate the CNS effects of INVEGA SUSTENNA®</td>
<td>INVEGA SUSTENNA® should be used with caution in combination with other centrally acting drugs and alcohol [see Adverse Reactions].</td>
<td>Monitor orthostatic vital signs in patients who are vulnerable to hypotension [see Warnings and Precautions].</td>
</tr>
<tr>
<td>Drugs with Potential for Inducing Orthostatic Hypotension</td>
<td>Because INVEGA SUSTENNA® has the potential for inducing orthostatic hypotension, the concomitant use of drugs that may decrease the effects of paliperidone [see Clinical Pharmacology (12.3) in Full prescribing Information]</td>
<td>Avoid using CYP3A4 and/or P-gp inducers with INVEGA SUSTENNA® during the 1-month dosing interval, if possible. If administering a strong inducer is necessary, consider managing the patient using paliperidone extended-release tablets [see Dosage and Administration (2.9) in Full prescribing Information].</td>
<td>Monitor orthostatic vital signs in patients who are vulnerable to hypotension [see Warnings and Precautions].</td>
</tr>
<tr>
<td>Levodopa and Other Dopamine Agonists</td>
<td>Paliperidone may antagonize the effect of levodopa and other dopamine agonists</td>
<td>Monitor and manage patient as clinically appropriate.</td>
<td></td>
</tr>
</tbody>
</table>

**INVEGA SUSTENNA® (paliperidone palmitate) extended-release injectable suspension, for intramuscular use**

**Table 7: Extrapyramidal Symptoms (EPS)-Related Conditions**, *MedDRA Preferred Term—Schizophrenia Studies in Adults*

**Table 8: Extrapyramidal Symptoms (EPS)-Related Conditions**, *MedDRA Preferred Term—Schizophrenia Studies in Adults*

**Table 9: Extrapyramidal Symptoms (EPS)-Related Conditions**, *MedDRA Preferred Term—Schizophrenia Studies in Adults*

**Table 10: Extrapyramidal Symptoms (EPS)-Related Conditions**, *MedDRA Preferred Term—Schizophrenia Studies in Adults*
INVEGA SUSTENNA® (paliperidone palmitate) extended-release injectable suspension, for intramuscular use

Animal Data
There were no treatment-related effects on the offspring when pregnant rats were injected intramuscularly with paliperidone palmitate extended-release during the period of organogenesis at doses up to 250 mg/kg, which is 10 times MRHD of 234 mg paliperidone based on mg/m² body surface area. In animal reproduction studies, there were no increases in fetal abnormalities when pregnant rats and rabbits were treated orally with paliperidone during the period of organogenesis with 4 times the MRHD of 12 mg based on mg/m² body surface area. Additional reproduction toxicity studies were conducted with orally administered risperidone, which is extensively converted to paliperidone. Dose palatal was observed in the offspring of pregnant mice treated with risperidone at 0.3 to 4 times the MRHD of 16 mg based on mg/m² body surface area; maternal toxicity occurred at 4 times the MRHD. There was no evidence of teratogenicity in embryo-fetal developmental toxicity studies with risperidone in rats and rabbits at doses up to 4 times the MRHD of 16 mg/day risperidone based on mg/m² body surface area. When the offspring of pregnant rats, treated with risperidone at 0.6 times the MRHD based on mg/m² body surface area, reached adulthood, learning was impaired. Increased neuronal cell death occurred in the fetal brains of the offspring of pregnant rats treated at 0.3 to 2 times the MRHD, the postnatal development and growth of the offspring was delayed. In rat reproduction studies with risperidone, pup deaths occurred at oral doses which are less than the MRHD of risperidone based on mg/m² body surface area, it is not known whether these deaths are due to a direct effect on the fetuses or pups or, to effects on the dams (see Risperdal® package insert).

Lactation
Risk Summary
Limited data from published literature report the presence of paliperidone in human breast milk. There is no information on the effects on the breastfed infant or the effects on milk production; however, there are reports of sedation, failure to thrive, jitteriness, and extrapyramidal symptoms (tremors and abnormal muscle movements) in breastfed infants exposed to paliperidone's parent compound, risperidone (see Clinical Considerations). Paliperidone has been detected in plasma in adult subjects up to 126 days after a single-dose administration of INVEGA SUSTENNA® (see Clinical Pharmacology (12.3) in Full Prescribing Information), and the clinical significance on the breastfed infant is not known. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for the drug and any adverse effects on the breastfed child from INVEGA SUSTENNA® or from the mother's underlying condition. Clinical Considerations Infants exposed to INVEGA SUSTENNA® through breastmilk should be monitored for excess sedation, failure to thrive, jitteriness, and extrapyramidal symptoms (tremors and abnormal muscle movements).

Females and Males of Reproductive Potential
Intrauterine
Females
Based on the pharmacologic action of paliperidone (D2 receptor antagonism), treatment with INVEGA SUSTENNA® may result in an increase in serum prolactin levels, which may lead to a reversible reduction in fertility in females of reproductive potential (see Warnings and Precautions (5.10)).

Pediatric Use
Safety and effectiveness of INVEGA SUSTENNA® in patients < 18 years of age have not been established.

Juvenile Animal Studies
In a study in which juvenile rats were treated with oral paliperidone from days 24 to 73 of age, a reversible impairment of performance in a test of learning and memory was seen, in females only, with a no-effect dose of 0.63 mg/kg/day, which produced plasma levels (AUC) of paliperidone similar to those in adolescents dosed at 12 mg/day. No other consistent effects on neurobehavioral or reproductive development were seen up to the highest dose tested (2.5 mg/kg/day), which produced plasma levels of paliperidone 2.3 times those in adolescents.

Juvenile dogs were treated for 40 weeks with oral risperidone, which is extensively metabolized to paliperidone in animals and humans, at doses of 0.31, 1.25, or 5 mg/kg/day. Decreased bone length and density were seen with a no-effect dose of 0.31 mg/kg/day, which produced plasma levels (AUC) of risperidone plus paliperidone 2.3 times those in adolescents.

Juvenile dogs were treated for 48 weeks with oral risperidone, which is extensively metabolized to paliperidone in animals and humans, at doses of 0.31, 1.25, or 5 mg/kg/day. Decreased bone length and density were seen with a no-effect dose of 0.31 mg/kg/day, which produced plasma levels (AUC) of risperidone plus paliperidone 2.3 times those in adolescents.

Juvenile dogs were treated for 48 weeks with oral risperidone, which is extensively metabolized to paliperidone in animals and humans, at doses of 0.31, 1.25, or 5 mg/kg/day. Decreased bone length and density were seen with a no-effect dose of 0.31 mg/kg/day, which produced plasma levels (AUC) of risperidone plus paliperidone 2.3 times those in adolescents.

Geriatric Use
Clinical studies of INVEGA SUSTENNA® did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. This drug is known to be substantially excreted by the kidney and clearance is decreased in patients with renal impairment (see Clinical Pharmacology (12.3) in Full Prescribing Information), who should be given reduced doses. Because elderly patients are more likely to have decreased renal function, adjust dose based on renal function (see Dosage and Administration (2.4) in Full Prescribing Information).

Renal Impairment
Use of INVEGA SUSTENNA® is not recommended in patients with moderate or severe renal impairment (creatinine clearance < 50 mL/min). Dose reduction is recommended for patients with mild renal impairment (creatinine clearance 30 to < 50 mL/min) (see Dosage and Administration (2.5) and Clinical Pharmacology (12.3) in Full Prescribing Information).

Hepatic Impairment
INVEGA SUSTENNA® has not been studied in patients with hepatic impairment. Based on a study with oral paliperidone, no dose adjustment is required in patients with mild or moderate hepatic impairment. Paliperidone has not been studied in patients with severe hepatic impairment (Clinical Pharmacology (12.3) in Full Prescribing Information).

Patients with Parkinson's Disease or Lewy Body Dementia
Patients with Parkinson's Disease or Lewy Body Dementia can experience increased sensitivity to INVEGA SUSTENNA®. Manifestations can include confusion, agitation, autonomic instability with frequent falls, extrapyramidal symptoms, and clinical features consistent with neuroleptic malignant syndrome.

DRUG ABUSE AND DEPENDENCE
Controlled Substance
INVEGA SUSTENNA® (paliperidone palmitate) is not a controlled substance.

Abuse
Paliperidone has not been systematically studied in animals or humans for its potential for abuse.

Dependence
Paliperidone has not been systematically studied in animals or humans for its potential for tolerance or physical dependence.

INVEGA SUSTENNA® (paliperidone palmitate) extended-release injectable suspension, for intramuscular use

OVERDOSAGE
Human Experience
No cases of overdose were reported in premarketing studies with INVEGA SUSTENNA®. Because INVEGA SUSTENNA® is to be administered by healthcare professionals, the potential for overdose by patients is low.

While exposure with paliperidone overdose is limited, among the few cases of overdose reported in premarketing trials with oral paliperidone, the highest estimated ingestion was 405 mg. Observed signs and symptoms included extrapyramidal symptoms and gait unsteadiness. Other potential signs and symptoms include those resulting from an exaggeration of paliperidone’s known pharmacologic effects, i.e., drowsiness and sedation, tachycardia and hypotension, and QT prolongation. Torsades de pointes and ventricular fibrillation have been reported in a patient in the setting of overdose with oral paliperidone.

Paliperidone is the major active metabolite of risperidone. Overdose experience reported with risperidone can be found in the OVERDOSAGE section of the risperidone package insert.

Management of Overdose
In the event of overdose, supportive and symptomatic measures should be given. There is no specific antidote to paliperidone.

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DOSAGE AND ADMINISTRATION
Controlled Substance
INVEGA SUSTENNA® (paliperidone palmitate) is not a controlled substance.

Abuse
Paliperidone has not been systematically studied in animals or humans for its potential for abuse.

Dependence
Paliperidone has not been systematically studied in animals or humans for its potential for tolerance or physical dependence.
It’s a Small World, After All

The classic song by the Sherman Brothers makes a good point: “It’s a world of laughter, a world of tears. It’s a world of hopes and a world of fears. There’s so much that we share. That it’s time we’re aware. It’s a small world after all.” Certainly, the events of 2021—including the continued struggles with the COVID-19 pandemic, climate change, and political unrest in various countries—made us acutely aware of the ripple effects of events across the globe. In this issue of *Psychiatric Times™*, we take this notion a bit further and explore global psychiatry.

Chaired by Editorial Board member Renato D. Alarcón, MD, MPH, emeritus professor of psychiatry at Mayo Clinic College of Medicine in Rochester, Minnesota, our special report dips into the deep waters of global psychiatry as the world marches forward into a new year. Milton L. Wainberg, MD, founding chair of the American Psychiatric Association’s Caucus of Global Mental Health, sets the stage by exploring the challenges and opportunities facing global psychiatry in a postpandemic world. Similarly, Richard F. Mollica, MD, MAR, director of the Harvard Program in Refugee Trauma and a professor of psychiatry at Harvard Medical School in Boston, Massachusetts, tackles the growing refugee crisis resulting from continued political unrest, violence, and disruptions due to climate change and related catastrophes.

Meanwhile, here in the United States and abroad, we continue to experience a mental health epidemic, with long waits for care, issues in treatment resistance, and untold unnecessary suffering. This issue’s clinical articles aim to provide you with the insights and tools required to address your patients’ needs and improve care. For instance, “TMS: A Useful Clinical Tool for Treatment-Resistant Depression,” by Abijith Ramanujam, MD, MPH, explores the promising treatment of transcranial magnetic stimulation (TMS). According to data, two-thirds of patients who receive TMS experience either full remission of or noticeable improvements in their depression, patients with depression have heard about Stanford Accelerated Intelligence (TMS). According to data, two-thirds of patients who receive TMS experience either full remission of or noticeable improvements in their depression.

As we move into the holiday season and look forward to a new year, it is exciting to think of promising new treatment strategies and protocols for the millions of individuals across the globe who struggle with psychiatric illness. As always, welcome to cover, *Psychiatric Times™* is committed to providing you with clinical insights, engaging commentaries and columns, and the tools and support you need to provide the best care to your patients.

Here’s to a wonderful 2022! ☃️

Mike Hennessy Sr
Chairman and Founder, MJH Life Sciences™
Is That Drug a Partial Agonist or a Partial Agonist?

John J. Miller, MD  Editor in Chief

In every branch of science, nomenclature plays a vital role in allowing a common language to be employed so that a clear and consistent meaning is applied to any term that is routinely used. Such is the case when describing the mechanism of action of a particular drug at a particular receptor—or so it used to be. The title of this editorial may appear to contain a typographical error, but it does not: It is exactly as I wrote it. As the science behind receptor pharmacology has become increasingly complex, a common term currently used to describe a receptor mechanism of action—partial agonism—has served to confuse rather than clarify the mechanism of many drugs placed in this category.

When a Drug Meets a Receptor

All drugs—in fact, all molecules—have a specific binding affinity for a specific receptor in a prespecified chemical environment. This is commonly referred to as the drug’s inhibition constant (Ki) at a particular receptor and is usually written as a concentration in nanomoles (nM). The FDA-approved product insert of every drug lists the Ki’s at all relevant receptors in Section 12—Clinical pharmacology, subsection 12.2—Pharmacodynamics. The smaller the Ki at a particular receptor, the tighter the drug binds to that specific receptor.

For example, let us say drug X has a Ki = 1 nM at the dopamine-2 receptor (D2R) and a Ki = 100 nM at the histamine-1 receptor (H1R). That translates clinically into a mechanism of action whereby drug X is very potent at the D2R, but 100-fold weaker at the H1R. If drug X is an antagonist at these 2 receptors, this predicts with high likelihood that drug X would be a good antipsychotic, but a weak antihistamine. If the antagonist drug Y, on the other hand, has a Ki = 1 nM at the H1R and a Ki = 100 nM at the D2R, drug Y should be a great antihistamine, but a weak antipsychotic.

The Ki gives us an important piece of information, but it does not tell us the complete story about what that drug is actually doing at a particular receptor—only how tightly it is binding. Many psychiatric medications bind to multiple receptors from the same or different neurotransmitter systems. To clarify, Ki’s are determined in vitro, and they can vary from one assay to another due to the properties of each assay (eg, pH, ion concentrations, temperature, and other physical chemistry properties). This explains why we can see a range of Ki’s for the same drug at the same receptor from different studies.

Despite these differences, the general properties of a drug at various receptors remains consistent across different assays. (Nonetheless, this situation supports the strong need for developing a Ki database based on exactly the same assay conditions for each drug/receptor studied.) The good news is that following the 2003 publication of the Human Genome Project, the Human Genome has been completely sequenced. The human genome is now available in its entirety, and as such, researchers can now scan the genome to see exactly what receptors are expressed in specific tissues of interest. With this information, we can now begin to understand the mechanism of action of a given drug at its specific target.

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Exploring the Consequences of the COVID-19 Pandemic
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Issues in Women’s Health: Global Lessons, Opportunities, and Challenges
Florence Thibaut, MD, PhD
Introducing an associated comorbidity of adult ADHD—amotivational features and chronic fatigue

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

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

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

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

References:
mine the binding affinities of drugs that will be used in humans are now cloned from the human genome. In years past, it was common to use rat, mouse, rabbit, or monkey receptors, which are not predictably analogous, structurally, to the corresponding human receptors.

How Does the Drug Impact Receptor Functioning?
Once we have determined the Ki of a specific drug at a specific receptor in a well-defined and reproducible chemical environment (assay), the next step is understanding how that drug changes the activity of the receptor. In the early days of pharmacology, it was simply a matter of determining if a drug appeared to agonize (activate) the receptor or antagonize (block) the receptor. Through decades of increasingly sophisticated research in many areas of basic science, our current understanding defines a wide spectrum of drug-receptor functional actions. Our current descriptions of drug-receptor activity that may occur when a drug binds to a receptor can be found in the Table.

Confusion of the Descriptor “Partial Agonism”
Let us focus on 2 of these mechanisms, both of which have been used interchangeably and, as a result, have confused the practicing clinician regarding what is actually going on at the drug-receptor interface in our patients’ brains: partial agonism (PA) and antagonism/partial agonism (AT/PA). When I was receiving my biochemistry training, these descriptors clearly differentiated 2 distinct mechanisms of action of a drug.

A PA would bind to a receptor of an endogenous neurotransmitter (EN) and provide some degree of agonism, but less than a full agonist—it would function the same as the EN. Hence, in the absence of the EN, the PA would provide some degree of receptor stimulation. In the presence of the EN, the PA would synergize with the EN and increase the overall agonism to some degree. If the EN was at 100% occupancy of its receptor, the PA would contribute very little.

An AT/PA drug provides both of these functions simultaneously. Clinically useful AT/PA drugs have binding affinities at the target receptor that are much stronger than the binding affinity of the EN. This combination of AT and simultaneous PA at the EN receptor allows for a predictable pharmacodynamic effect if the AT/PA is dosed to occupy 100% of the target receptor. At full AT, the percent of PA determines the functional activity of the EN receptor. If the AT/PA has 10% PA, it functions as an antagonist. If the AT/PA has 90% PA, it functions as an agonist. Consequently, you could create a series of AT/PA drugs that all share the same potent AT, but their PA would range from 1% to 99%. When dosed to 100% antagonism, the percent PA would determine the functional activity of that receptor. This allows for a predictable effect at the EN receptor.

AT/PA and the Opioid Receptor
Buprenorphine is a commonly prescribed drug that has a predictable effect on an individual who is using opioid(s), based on its activity as an AT/PA at the mu opioid receptor (MOR). Understanding its AT/PA provides an exemplary model of how this combination of receptor effects manifests clinically. PET scans on live human brains have demonstrated that buprenorphine occupies close to 100% of the MORs at doses between 18 mg and 24 mg per day, depending on the patient. Like naltrexone, naloxone, and samidorphan, buprenorphine is a potent antagonist at the MOR, but unlike the other 3, it also has functional simultaneous partial agonism approximately equal to 20 mg of methadone at full MOR occupancy. Being a potent antagonist at the MOR, buprenorphine displaces endorphins and most mu opioid agonists, including morphine, heroin, oxycodone, oxymorphone, hydrocodone, hydrodorphone, and methadone. This combined AT and PA is the pharmacological reason buprenorphine is such a successful drug in the treatment of opioid use disorders.

Any seasoned buprenorphine prescriber will tell you that adding 24 mg of buprenorphine to an individual’s regimen when that person has been taking more than 30 mg of methadone for several months will result in immediate severe opioid withdrawal. The potent antagonism prevents other mu opioid agonists from synergistically increasing buprenorphine’s agonism at the MOR. Referring to buprenorphine as a PA does not convey the complexity of what is happening at the MOR: potent antagonism that displaces endorphins and most opioid agonists, while simultaneously partially agonizing the MOR with approximately 20-mg equivalents of methadone.

AT/PA and the Dopamine-2 Receptor
All antipsychotics, both typical (first generation) and atypical (second generation), are pure D2R antagonists except for 3: aripiprazole, brexiprazole, and cariprazine. These 3 are sometimes called “third generation” due to their shared property of antagonism at the D2R. This mechanism of action at the D2R creates different pharmacological rules than those we apply for the other antipsychotics, Referring to these 3 antipsychotics as PAs could create a great deal of confusion about their mechanism of action as well as how to dose them when cross-titrating from a pure antagonist or when they are used in combination therapy.

Concluding Thoughts
When prescribing medications, a clinician relies on a drug’s defined pharmacokinetic and pharmacodynamic properties, involving numerous factors, to make informed choices as to what medication to use. One of those factors is the mechanism of action occurring at the various drug-receptor interfaces. The

Table. Descriptions of Drug–Receptor Activity

- **Agonism (A)**
- **Antagonism (competitive vs noncompetitive or uncompetitive) (AT)**
- **Partial agonism (PA)**
- **Antagonism/partial agonism (AT/PA)**
- **Inverse agonism (IA)**
- **Positive allosteric modulation (PAM)**
- **Negative allosteric modulation (NAM)**

"Referring to these 3 antipsychotics as PA creates a great deal of confusion about their mechanism of action as well as how to dose them when cross-titrating from a pure antagonist or when they are used in combination therapy.”

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

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

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

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

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

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

Risk in Patients With Impaired Respiratory Function
• Closely monitor patients taking LOREEV XR for impaired respiratory function, and consider discontinuing it if signs and symptoms of respiratory depression or apnea occur.

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

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

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

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

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

Please see the accompanying Brief Summary.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(Cont’d)
Immune System Disorders: anaphylactoid reactions, hypersensitivity reactions;

Investigations: increase in bilirubin, increase in liver transaminases (including elevated LDH), increase in alkaline phosphatase; Metabolism and Nutrition Disorders: change in appetite, hyponatremia;

Nervous System Disorders: ataxia, autonomic manifestations, coma, convulsions/seizures, drowsiness, dysarthria/slurred speech, extrapyramidal symptoms, headache, tremor, vertigo, memory impairment;

Psychiatric Disorders: amnesia, change in libido, confusion, decreased orgasm, depression, disinhibition, disorientation, euphoria, suicidal ideation/attempt, unmasking of depression;

Reproductive System and Breast Disorders: impotence;

Respiratory Thoracic and Mediastinal Disorders: apnea, respiratory depression, worsening of obstructive pulmonary disease, worsening of sleep apnea;

Skin and Subcutaneous Tissue Disorders: allergic skin reactions, alopecia, dermatological symptoms.

Paradoxical reactions—including anxiety, excitement, agitation, hostility, aggression, rage, sleep disturbances/insomnia, sexual arousal, and/or hallucinations—may occur.

Small decreases in blood pressure and hypotension have been reported with immediate-release lorazepam.

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

USE IN SPECIFIC POPULATIONS

Pregnancy

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

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

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

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

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

DRUG ABUSE AND DEPENDENCE

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

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

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

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

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

Tolerance
Tolerance to LOREEV XR may develop from continued therapy.

OVERDOSAGE

Clinical Experience
In postmarketing experience, overdose with lorazepam has occurred predominantly in combination with alcohol and/or other drugs. Manifestations of overdose include varying degrees of CNS depression, ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion, paradoxical reactions, dysarthria, and lethargy. In more serious cases, symptoms may include ataxia, hypotonia, hypotension, cardiovascular depression, respiratory depression, hypnogotic state, coma, and death. In case of an overdosage, consult a Certified Poison Control Center at 1-800-222-1222 for latest recommendations.

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

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

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

Tolerance
Tolerance to LOREEV XR may develop from continued therapy.

OVERDOSAGE

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It’s Time for Us to Stop Waffling About Psychiatry

CRITICISM 1: Psychiatric illnesses are not real illnesses in the conventional sense because they are not physically and biologically real.

Critics point out that (with the possible exception of Alzheimer disorder and other dementias) neurobiological research has failed to identify the precise biological mechanism for mental illnesses. That is, research has failed to produce the holy grail of a central pathology for even a single major mental illness. They also point out that our DSM diagnostic categories may not, and probably do not, correspond to actual disease entities.

Why is this criticism wrong? Because critics breezily ignore the massive array of medical and neurobiological research on the nature of mental illness that has accumulated in the last 50 years. Major mental illnesses are also physical illnesses, and the evidence for this is overwhelming. For instance, hundreds of structural imaging studies have shown significant grey matter losses for major mental illnesses. Microscopic studies have also shown abnormalities, including hippocampal and parahippocampal pathology in depression, posttraumatic stress disorder, and schizophrenia. Genetic studies have shown positive associations to all major mental illnesses, including addiction, schizophrenia, and attention-deficit/hyperactivity disorder. Hormonal abnormalities have been found across major psychiatric disorders, and inflammation has been documented as well. While the holy grail of central pathophysiology has not been located, there is more than enough evidence to know that major mental health disorders include physical, biological dysfunction.

We do not have to know precisely how mental illness is physical to know beyond a reasonable doubt that it is physical. In light of current research, it is manifestly unreasonable to suggest otherwise. To put it another way, just because we do not know everything about the biology of mental illness does not mean that we don’t know anything about the biology of mental illness.

CRITICISM 2: Psychiatric medications make things worse. They are dangerous substances pushed by drug companies and greedy psychiatrists.

Psychiatric medications do indeed have serious risks. This is so because every medicine with actual medical effects has serious risks. As physicians, we know that common medications like aspirin and acetaminophen can cause fatal, sedatives like diphenhydramine can cause delirium and contribute to dementia, and that the widespread use of antibiotics carries a heavy price for public health. No medicine is risk free.

Does that mean psychiatric medications are foolish and unwarranted risks? Not necessarily. Every good physician, and every well-informed patient, must weigh the risks of any treatment against potential benefits. Psychiatriests know that we cannot compare the use of psychiatric medications with zero risks, but with the risks of not taking a medication at all. What are the risks of inadequately treated mental illness? Mental illness is devastating to both mind and body. It speeds up the aging process, reduces the lifespan by an average of 10 years, and disables patients at rates higher than most other types of medical illness. None of the top 25 most disabling medical illnesses are mental illnesses. Mental illness is also deadly, accounting for an estimated 14% of all deaths worldwide.

Meanwhile, there are well-proven psychiatric medications for all major mental disorders. What do I mean by well-proven? I mean proven by the same standards that apply to any other medical treatment, including multiple large, double-blind, placebo-controlled studies substantiating their use as reviewed by outside groups of experts and other interested parties. For instance, a review and meta-analysis of antipsychotic medications including 167 studies with 28,102 participants substantiated their use for schizophrenia. Although challenges have been made to the efficacy of antidepressants, one recent meta-analysis for acute treatment of depression included 522 studies with 116,477 subjects and found that “all antidepressants were more efficacious than placebo in adults with major depressive disorder.”

If psychiatric medications are effective, they are widely regarded as significantly less effective than medications in other branches of medicine. Yet a meta-analysis directly comparing the efficacy of psychiatric with general medical drugs found otherwise. Leucht and colleagues compared medications for 20 common general medical conditions with medications for 8 major psychiatric disorders. They found no statistical difference between the effect sizes of the 2 groups of medications. Overall, psychiatric medications are comparable with those for chronic medical conditions such as hypertension, asthma, and rheumatoid arthritis. Imagine, then, the hand-wringing and furious debate that would ensue if other medical treatments were treated with the same hostility, suspicion, and bias as psychiatric medications.

CRITICISM 3: Psychiatrists are biological reductionists and pill pushers, who diagnose and prescribe everyone they see regardless of their condition.

As psychiatrists, we recognize that employers, insurance companies, and government agencies tend to pressure us to provide only medical diagnosis and biological therapies, leaving other aspects of mental health care to other professionals. But the element of truth in this criticism masks a host of distortions and false assumptions. For instance, it is incorrect to say that psychiatrists believe only in...
biological realities, or that psychiatrists want to diagnose disease and push pills on every hapless patient. Critics often forget that psychiatrists do not prescribe the majority of psychiatric medications in this country.25 Beyond this, the pill-pusher narrative completely misses the broader medical and social contexts in which psychiatrists practice. There is a massive shortage of psychiatrists in this country and the world as a whole. This means that it is difficult to get in to see a psychiatrist, even for those patients with an urgent need. Even patients who can pay for treatment out of pocket will have to be persistent and determined to get treatment from a psychiatrist. And this, in turn, means that most individuals who finally get to see a psychiatrist suffer from significant, chronic illness, and most have already tried and failed more readily available treatments (such as self-help books, psychotherapy, and medications prescribed by primary care physicians). Ask yourself: How often do you see a new patient who has not tried and failed multiple interventions already? How often do you see a new patient who has not suffered from mental symptoms for years before ever getting a psychiatric evaluation? Like other medical specialists, psychiatrists usually treat patients with moderate-to-severe, chronic, and complex illnesses. And more severe and chronic psychiatric illness usually requires multimodal treatment, including psychotherapy and medication.

Given this context, it would be surprising if psychiatrists did not prescribe medications to the vast majority of their patients. Do you think that endocrinologists and rheumatologists prescribe medications to most of their patients? No one suggests that these specialists are greedy pill-pushers. Yet most critics of psychiatry reason in this very fashion. Furthermore, I do not personally know a single psychiatrist who claims that mental illness is only biological, or who insists that psychiatric medications are the only legitimate form of treatment.26 Instead, this criticism of psychiatry seems to be a compelling narrative that reflects divisions in our field, which were present in the 20th century, when biological psychiatrists and Freudians fought over psychiatric turf and legitimacy. Thanks to progress in scientific research, those days are long gone. Both medications and psychotherapy are well proven, with hundreds of studies legitimating the medical use of cognitive behavioral therapy, psychodynamic therapy, interpersonal therapy, dialectical behavioral therapy, mindfulness-based therapies, and many more.27 Every psychiatrist I have ever met supports the use of psychotherapy and other psychosocial treatments, and they recognize that psychosocial treatments are woefully under-funded for those with moderate-to-severe mental illness.

Concluding Thoughts

We live in an intellectual culture that has habituated the public to think of psychiatry as flawed, failed, corrupted, and lost. The stereotypical picture of our field focuses relentlessly on the influence of drug companies, the weaknesses of the DSM-5, and the dangers of overprescribing. But when this picture of our field dominates, the public loses sight of the authentic healing work that we and other mental health professionals perform on a daily basis. They forget the scientific realities that ground our field in something besides self-interest and profit and, therefore, the fault of the scientifically substantiated treatments that make our gratifying work possible. And when we as psychiatrists forget to confront and correct such one-sided distortions, the results are disastrous.

Before you finish this article, consider trying a thought experiment. Reflect for a moment and see if you can think of well-known intellectuals who are famous for being gadflies and critics of psychiatry. I would bet that a little effort would bring up a wide variety of names associated with everything from outright antipsychiatric to legitimate and constructive criticism: Tom Cruise; Thomas Szasz, MD; Robert Whitaker; Peter Breggin, MD; Allen Frances, MD.

But who, on the other hand, is a well-known proponent of psychiatry? Ask yourself whether you can name a similar list of individuals who are well-known defenders of our work. And if several names do not spring immediately to mind, what does this tell you about our profession? What does this tell you about the state of our culture in regard to our profession? What does this tell you about our intellectual habits and assumptions about mental health care by physicians? And finally, what does this realization call you to do in response to such a sad and twisted state of affairs?

Dr Morehead is the director of training for the general psychiatry residency at Tufts Medical Center. His new book, Science Over Stigma, promotes a defense of mental health treatment and a call for advocacy. Dr Morehead would like to thank Ronald Pies, MD, for his generous assistance with this article.

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the patient, his symptoms are comparable with a “living hell on earth.” Mr West had a history of illicit drug use—stimulant use—for a brief period in his early 20s but has not relapsed since. He describes a rich cultural background with life in different countries (accompanying his family as they moved), as well as medications and illicit substance use that are unfamiliar to you, prompting some frantic internet searching. At one point, he mentions fenethylline, which he felt had helped him “fight being tired,” but says he has not used it in about 7 years.

To tackle anxiety symptoms, he has been on a plethora of medications, all of which had adverse effects (AEs) and were discontinued. He has been fully adherent to all treatment recommendations, has never missed any of his appointments, and produces multiple negative urine drug screens. He is diligent in attending all of his psychotherapy sessions as well. Despite his symptoms, he maintains a job, pays his bills with no issues, and dedicates a lot of attention to his ailing mother. However, you note upon history-taking that he has no close friends and has not had romantic involvements, which he attributes to his symptoms: “I’m just not OK, doc, I tell you.” The patient is followed for 6 years.

**Year 1: Getting to Know the Patient**

The first year is spent establishing rapport and getting to know the patient. Monthly visits follow the same pattern; the patient profusely describes beliefs of having “something wrong” that is not properly diagnosed. He asks for brain imaging and cortisol levels, and he brings literature showing sustained brain damage from substance use. Attempts at reassurance often fall flat and are of limited effectiveness, but, as he is a model patient otherwise, you keep trying. Attempts at cognitive behavioral therapy produce limited positive effects, and the patient frequently comments, “This is too simple for me.”

You believe, based on his description, that he has irritable bowel syndrome (IBS), but he has never received specialized care. He reports that the fatigue and anxiety correlate with his gastrointestinal (GI) symptoms. He does slightly better when he is able to wake up between 9 and 10 AM; when he has to awaken earlier (ie, for work), he experiences loose bowels, burping, indigestion, and nausea.

At the end of year 1, Mr West tells you he has to seek “more care. I have to get answers—something is wrong with me.” He moves to another country in the hopes of more thorough treatment. He returns in 2 years, and you are surprised to see his name appear on your clinic roster.

**Years 3 and 4: The Return**

Out of the blue, Mr West returns, bringing with him a panoply of medical test results, all of which are negative, as expected. He continues to report that he feels he has a terrible missed diagnosis, but he is less forceful in that statement and more amenable to reassurance. He continues to report daily GI symptoms and fatigue that severely limit his social interactions. Mr West mentions 2 medications that have been somewhat helpful, both of which you had to Google: Motival (fluphenazine and nortriptyline) and Deunxit (melitracen and fluoxetine). He continues to take fluoxetine, as he has done for years.

**Year 5: Addressing GI Issues**

In year 5, Mr West agrees to go to a GI specialty clinic. As a result, he changes his diet drastically, as well as medications and illicit substance use—stimulant use—for a brief period in 2 years, and you are surprised to see his name appear on your clinic roster.

**Diagnosis and Treatment**

Computational modeling confirms what clinicians already know: Evidence suggests that individuals with psychiatric illness such as depression and anxiety misread and misinterpret visceral information compared with healthy controls. As a result, a patient with anxiety may feel a benign physical symptom very acutely helpful with fatigue. At most sessions, however, he still reports his life is hell.

**Exploring Epidemiology**

Generalized anxiety disorder (GAD) is characterized by exaggerated tension, worrying, and nervousness about daily life events. GAD is often a lifelong disease, causing significant impairment. The prevalence of anxiety disorders in the United States is approximately 10% in adults and 19.1% in adolescents (Figures 1 and 2). Symptoms include restlessness, irritability, and fatigue, with overthinking and consideration of worst-case scenarios predominating cognitive schemas of GAD patients. Patients with anxiety frequently have GI symptoms (about 18% of individuals).

Individuals with IBS are twice as likely to have physical fatigue, GI-specific anxiety, perceived stress, pain catastrophizing, and trait anxiety. More severe mental symptoms and distress are associated with IBS severity, and vice versa.


<table>
<thead>
<tr>
<th>Overall</th>
<th>Female</th>
<th>Male</th>
<th>18-29</th>
<th>30-44</th>
<th>45-59</th>
<th>60+</th>
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<tbody>
<tr>
<td>2.7%</td>
<td>3.4%</td>
<td>1.9%</td>
<td>2.0%</td>
<td>3.5%</td>
<td>3.4%</td>
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</tbody>
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and interpret the symptom in a catastrophizing way, instead of dismissing it as normal. A relevant concept is body awareness.7 Somatic internal perceptions—which are often unconscious—involve interoception and proprioception, and these neurological paths can be altered or damaged by disease processes. Those sensations arise to consciousness and are interpreted by the individual, with an assigned explanation for the sensation in question. Thus, when dealing with patients who have anxiety and comorbid somatic symptomatology, the clinician may be faced with somatosensory amplification and potential exaggerated or maladaptive interpretation of bodily symptoms. This is a budding research field, with further definitions and clarification of terminology needed.

Patients with anxiety disorders have a tendency to avoid making changes to their medications, as trying new things and making alterations to their routine makes them apprehensive. This may make them more likely to report AEs after trying new treatment options, which could explain why this patient had low symptomatic tolerance to many of the attempted alternate treatments. It is important to give patients with anxiety disorders ample time to adapt to changes in their treatment regimens. Forcing change, or switching too rapidly, may be counterproductive and could create apprehension, possibly worsening anxiety and creating a barrier to adherence. Slow dosing and upward titration are essential to avoid AEs and a mental aversive reaction to treatment.

"Out of the blue, Mr. West returns, bringing with him a panoply of medical test results, all of which are negative, as expected."

**Treatment Selection**

It is sometimes difficult to unravel all aspects of a clinical case within a few visits. Intrusive personality aspects can underlie much of the behavior. For example, the patient’s mother had anxiety and comorbid somatic symptomatology, the clinician may be faced with somatosensory amplification and potential exaggerated or maladaptive interpretation of bodily symptoms. This is a budding research field, with further definitions and clarification of terminology needed.

Supplementation with serotonin-norepinephrine reuptake inhibitor as first-line treatment, with augmenting agents such as the azapirone (like buspirone) and antihistamines (like hydroxyzine). Only 1 antipsychotic—trifluoperazine—is approved by the US Food and Drug Administration for use in treating anxiety, although off-label use of multiple antipsychotic agents is very prevalent in clinical practice. GABAergic agents are also profusely used with some success. Serotonergic mechanisms are important, given the presence of serotonin receptors throughout the gut and the known dysregulation of serotonergic afferent neural signals in functional GI disorders.

In terms of dosing, clinicians anecdotally note that some patients with anxiety seem to require multiple doses of medications, even for those agents that can be dosed once daily. This is another clinical correlate of anxiety that may be unrelated to treatment, but more linked to patient satisfaction, as systematic reviews show that most classes of psychotropics can be dosed once daily without a decrease in efficacy.

In this case, the patient did well on Deansit and Motival, each of which combines an antipsychotic medication and an antidepressant medication. A positive response to Deansit and sertraline vs sertraline alone has been shown in patients with chronic somatic diseases, so this could explain the success of the regimen in this patient. Mr West continued to be stressed about having to ask people to get his medication when they travel and wanted a substitute. He achieved the best results with chlorpromazine, which is chemically similar to the flupentixol in Deanxit.
GLOBAL PSYCHIATRY

Social Determinants and Clinical Realities

Renato D. Alarcón, MD, MPH

There is little doubt that globalization is among the most prominent topics of discussions. Many factors have contributed to this development, but advances in communication and transportation, as well as migrations across the world, are considered its main sources. Thus, globalization exhibits a rather ambiguous image of glorious machine-based achievements and profoundly uncertain—and at times, chaotic—human experiences. Mental health is a crucial component of the new “global reality.”

Global mental health (GMH) is an important field, because of the various challenges that humanity confronts. Every human experience tests mental health resources and engenders possibilities of success as well as risks of failure, with clinical consequences, symptoms, syndromes, or disorders that require management intervention. Solid knowledge, diagnostic processes, treatment resources, and ethical norms are— or should be—the same all over.

Several organizations have responded to the challenge, calling for public and mental health measures, universal health coverage, prevention and treatment of specific conditions, etc. GMH principles imply that all physicians—especially psychiatrists—who encounter patients from different socioeconomic, geographic, ethnic or cultural backgrounds in our global village must be familiar with the global social determinants of health, the substantial features of an integrated (bio-psycho-socio-cultural) care approach, and the funding and equipment gaps that reflect the world has not responded to the evidence. A prominent world mental health figure affirmed that “all countries are ‘developing’ when it comes to mental health,” and that we must go “beyond addressing the treatment gap to also reduce the prevention, care and quality gaps to reduce the global burden of mental health problems.”

This Special Report attempts to cover few areas of the current GMH scenario. The refugee crisis shows a dramatic, transcontinental impact with high levels of posttraumatic stress disorder from a variety of incidents. Maslow’s Hierarchy of Needs and the H-5 Model offer wise options of social and clinical interventions.

Similarly, another article analyzes the GMH consequences of the COVID-19 pandemic. Distinctions between high- and low-income countries are discussed as well as the ongoing debates on the causality of the mental and emotional symptoms in survivors.

Finally, another article discusses the problematic challenges that GMH faces now and in the future, along with cogent foundations to approach proposed solutions.

Mental health is relevant to people in all countries, particularly those who are vulnerable. The commitment of mental health professionals to improve the situation across the world is as important as the responsibilities of governments and health authorities to improve the impact of social determinants, implement evidence-based interventions, increase mental health investments, and support multifaceted research initiatives.

Two final points must be made. The first is to emphasize the importance of cultural psychiatry principles in training programs and practice settings of specialists; these components assist not only in a better understanding of the suffering of different cultural groups brought to us by globalization, but also help erase the prejudices of a pervasive Otherness and its discriminatory, stigmatizing arms. The second issue is the need to pursue systematic research topics in GMH aimed at the delineation of bioepigenetic and clinical differences among patients with similar diagnoses and diverse backgrounds. These research initiatives must extend to international collaboration in laboratories, clinical settings, and public health offices in search of comprehensive global policies of mental health care.

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ALSO IN THIS SPECIAL REPORT

Exploring the Consequences of the COVID-19 Pandemic
Professor Sir Graham Thornicroft, PhD, MSc

Issues in Women’s Health: Global Lessons, Opportunities, and Challenges
Florence Thibaut, MD, PhD
Introducing an associated comorbidity of adult ADHD—the need to quiet a hyperactive mind

There is a significant overlap between adult ADHD and substance use disorder (SUD)\cite{1,2}

SUD is prevalent in adults with ADHD, and may relate to the core symptoms of the disorder.\cite{1,3} In fact, risk for SUD has been found to be double for individuals with ADHD vs those without:\cite{4}

- Approximately 50% of adolescents and adults with SUD also have ADHD, which generally develops first.\cite{5}
- 39% of adults newly diagnosed with ADHD were found to have SUD in a multicenter survey.\cite{1}

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

Of the core ADHD symptoms, hyperactivity/impulsivity have shown a more robust relationship with the abuse of alcohol and tobacco.\cite{4}

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

References:
Moving Beyond the Enormity Problem: Tackling the Global Refugee Crisis

Richard F. Mollica, MD, MAR

The world is facing global crises of catastrophic magnitude. Paradoxically, while modern psychiatry is entering a golden age, with many scientific and cultural advances leading to effective low-cost care for common illnesses such as anxiety and depression, and less stigma associated with mental health disorders, the global catastrophes facing every person have led to a collective trauma. Healers and sufferers are now universally affected—no one is safe—creating a new solidarity of mutually concerned interests that, if mobilized, could lead to the establishment of new and powerful co-constructed relationships and actions. Old ideas need to be discarded, and new solutions imagined, studied, and implemented. The world is at a crossroads, and the psychiatric profession can be at the vanguard of offering a new vision. In this brief review of one of the major global crises facing humanity—the refugee crisis—a new vision of psychiatric care is considered. This vision, presented to the National Academy of Medicine in 2016, has since matured, as we have been forced to confront major crises facing all of us.

These historical crises, which include climate change and “ecocide,” the COVID-19 pandemic, and refugee displacement due to conflict or environmental degradation, feel like a slow-moving train wreck that is impacting our collective sense of health and well-being. The impact on the younger generations is especially concerning. Psychiatry can play a major role in addressing public anxiety and fear related to the “enormity problem.” ABC News correspondent Bill Blakemore—who has reported on war, conflict, and climate change for more than 4 decades—uses this term to describe problems so big that solutions are impossible to comprehend. The enormity problem leads to feelings of hopelessness and despair; a future horizon does not exist. This sense of enormity may lead us to become metaphorically unconscious when considering what—if anything—can be done to alleviate these problems. Mental practitioners are faced with the following realities:

**Ecocide**

According to the United Nations Environment Programme, the Earth is in the midst of a mass extinction of life, with 100 to 200 species of plants, insects, birds, and mammals becoming extinct every day. This loss is considered to be the largest extinction of life since the that of the dinosaurs 65 million years ago. Environmental degradation linked to climate change has a major impact on displacement, poverty, and sustainable development. The planet is already 1.1 °C warmer than in the preindustrial period, and it will be 1.5 °C warmer by 2040. Carbon dioxide is at its highest level in the past 2 million years; sea levels are rising faster than in the past 3000 years; and ice is at its lowest in 1000 years. The world will continue to experience catastrophic storms, droughts, wildfires, and rising sea levels. The United Nations (UN) estimates that more than 70 million persons have already left their homes due to extreme weather events. It is believed that 1 billion persons will be displaced because of climate change by 2040. The absolute number of persons living in informal settlements or shantytowns is already more than 1 billion. These environments are characterized by air pollution, poor waste disposal, and lack of public green spaces and health services, especially mental health services. The UN has recognized that climate change, environmental degradation, and natural disasters are interacting to create historic increases in levels of mass migration. Filippo Grandi, UN High Commissioner for Refugees (UNHCR), noted:

> We need to invest now in preparedness to mitigate future protection needs and prevent further climate-caused displacement. Waiting for disaster to strike is not an option.

**COVID-19 Pandemic**

The COVID-19 pandemic has impacted the world in a way not seen in more than a century. There are more than 230 million confirmed cases in 221 countries and territories and 4.8 million deaths at the time of this writing. The United States has sustained more than 44 million cases and more than 700,000 deaths. The pandemic has been exacerbated by racial trauma, bringing the health disparities in communities of color to the forefront. The pandemic has negatively affected the mental health of people worldwide, with an extreme impact on refugees and displaced persons. In many countries such as India, Iran, Nepal, and Afghanistan, it has led to displacement of tens of thousands of people. Simultaneously, the mental health impact on the world’s health care practitioners has been dramatic. Psychiatry has been stepping up to meet the growing demands for COVID-19-related mental health services. For instance, at my institutions (Massachusetts General Hospital and Harvard University), caring for those who have cared for others is a top priority.

**Tackling the Refugee Crisis**

According to UNHCR, there are now 82.4 million displaced persons worldwide, including 35 million children (Figure 1). This number includes 48 million internally displaced people, 26.4 million refugees, 4.1 million asylum seekers, and 3.9 million Venezuelans displaced abroad. This represents the largest number of persons on the move since World War II. The rapid destruction of the natural

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**Figure 1. A Snapshot of Refugees Worldwide**

- **68%** originate from just five countries
- **39%** hosted in just five countries

More than two thirds of all refugees under UNHCR’s mandate and Venezuelans displaced abroad come from just five countries (as of end-2020).

Turkey hosts the largest number of refugees, with nearly 3.7 million people. Colombia is second with 1.7 million, including Venezuelans displaced abroad (as of end-2020).

**Figure 2. The New Definition of Health**

“Health is a personal and social state of balance and well-being in which people feel strong, active, wise and worthwhile; where their diverse capacities and rhythms are valued; where they may decide and choose, express themselves and move about freely.”—Chetna, Gujarat, India

The new definition is an integrated holistic concept focusing on the creation of a healthy body, healthy mind, and healthy spirit (www.chetnaindia.org).
The Harvard Program in Refugee Trauma (HPRT) has been clinically caring for refugee survivors of mass violence and torture for more than 4 decades, caring for the health and mental health needs of more than 10,000 refugee patients in the United States and highly traumatized populations in Cambodia, Peru, Bosnia-Herzegovina, Croatia, Japan, Liberia, Lebanon, Italy, and Australia. Lessons learned over the past decades can help the fields of medicine and psychiatry to move beyond the enormity problem and serve as a model for the public health contribution to addressing the other global crises presented in this article. When HPRT established one of the first refugee clinics in the United States in 1981, little was known of refugee trauma and its impact on individuals, families, and communities. Refugee mental health was not considered important by international agencies responsible for the care of refugees. It was firmly believed that the refugee was like a rubber band, stretched by displacement: once returned home or resettled, the refugee would snap back to normal. In contrast, today refugee mental health is considered a priority by UNHCR and the World Health Organization (WHO). In my National Academy of Medicine presentation (before the COVID-19 pandemic), several major themes were addressed. The WHO definition of health—“a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity”—was expanded using the women’s health approach by Chetna (www.chetnaindia.org) to a more integrated holistic concept focusing on the creation of health that emphasized a healthy body, healthy mind, and healthy spirit for all people. Respect for personal and community agency, freedom from prejudice and stigma, and social justice were emphasized (Figure 2).

This new definition places importance on eliminating structural violence and social injustice, expanding access to schooling for children and education for women, and ending gender-based violence. The climate change crisis further highlights the need for environmental justice, including the right to access clean water, fresh air, and green spaces. Major efforts to stop the poaching and industrial harvesting of wildlife and native plants need to be added. This question must be answered: Can a human being be healthy in an environmentally degraded environment?

Tremendous advances have been made in scientifically and culturally validating the mental health impact of refugee trauma. Since the earliest population-based studies, the high prevalence of post-traumatic stress disorder (PTSD) and depression in refugee and war-surviving civilians has been consistently demonstrated. In a meta-analysis of epidemiologic studies, researchers showed that countries with a recent war history (1989-2018) yielded point-prevalence rates of PTSD of 26.5% and of major depression of 23.3%; of those who pre-

ried to the Maslow model to create an evidence-based approach to restore individuals from traumatized status to wellness. 

Figure 5. Abraham Maslow’s Hierarchy of Needs

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Figure 6, the core of which is the “trauma story.” All 5 dimensions are anchored in a common thread of the trauma story, ie, the personal life story and narrative of the survivor of human violence. Listening empathically is a key component of healing. The following is a brief synopsis of each area.

H1—HUMAN RIGHTS VIOLATIONS. All refugees have suffered human rights violations. These violations include gender-based violence and other unspeakable atrocities. Acknowledging and responding to human rights violations, including the pursuit of justice, are essential to the healing process.

H2—HUMILIATION. In most refugee situations,
humiliation is the primary goal of violence. Acts are used to create humiliation aimed at the physical, psychological, and cultural annihilation of the refugee community and society.

H3—SELF-HEALING. Self-healing is a natural process. In many refugee studies, altruism, work for (children, education), and spirituality are associated with increases in resiliency to violence.

H4—HEALTH PROMOTION. Extensive research has revealed the long-term impact of violence on health and mental health of the patient who has been traumatized, including chronic disease, diabetes, stroke, drug addiction, suicide, and chronic depression. Health promotion needs to be implemented early in the refugee experience.

H5—HABITAT. The term habitat encompasses the total environmental and cultural context of refugees and other traumatized persons, as distinct from the more limited concept of housing or shelter. The term derives from the Latin habitation, which refers to the natural environment of a person or the place where an organism dwells. Habitat, which is also described by the term built environment, is especially important for refugees because they often face terrible living conditions for years after they have fled their homes, leading to social disruption, emotional damage, and psychological stress.

Healing environments can be created for refugees and displaced individuals. Figure 7 illustrates the built environments created by the gifted architect Rabih Shibli, MA, and his team at the American University of Beirut in Lebanon for Syrian refugees because they often face terrible living conditions for years after they have fled their homes, leading to social disruption, emotional damage, and psychological stress. The WHO added the Mental Health Gap Action Programme (mhGAP) in 2008 for the diagnosis and treatment of psychiatric and substance use disorders in low- and middle-income countries, which was expanded to include humanitarian emergencies. Farag et al have clarified how the mhGAP can be made culturally sensitive, valid, and effective in varying cultural settings.

Summary

As can be seen, enormous advances in the cultural and scientific mental health care of refugees and displaced individuals have been made over the past 40 years. The impact and potential treatment of the social determinants of health/mental health in refugees—including gender-based violence, poverty, injustice, and human rights violations—have been identified. Now the global crises of climate change and the COVID-19 pandemic that are fueling global displacement and great human suffering need to be addressed upstream by psychiatry. The silos that exist between the current systems of health care, economic development, and humanitarian assistance need to be dismantled and the systems integrated. Mental health professionals, including psychiatrists, and their medical-psychiatric science must be integrated into each of these domains. Each development project needs to be linked to systems of health and mental health care. For example, all persons (not just refugees) need access to primary health care that includes integrated mental health care. Major global catastrophic crises are with us. But we can overcome our feelings of hopelessness and despair in the face of the enormity problem by working to restore to wellness those who have been damaged physically, mentally, and spiritually, and by advocating for public health solutions that can mitigate and prevent the root causes of the mental health crises facing the world today.

Dr Mollica is the Director of the Harvard Program in Refugee Trauma and a Professor of Psychiatry at Harvard Medical School.

REFERENCES

LYBALVI®
olanzapine and samidorphan
5 mg/10 mg, 10 mg/10 mg, 15 mg/10 mg, 20 mg/10 mg tablets

NOW AVAILABLE

For the treatment of adults with schizophrenia or bipolar I disorder

**Indications**
LYBALVI is indicated for the treatment of:
- Schizophrenia in adults
- Bipolar I disorder in adults
  - Acute treatment of manic or mixed episodes as monotherapy and as adjunct to lithium or valproate
  - Maintenance monotherapy treatment

**Important Safety Information**

**Boxed Warning:** Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. LYBALVI is not approved for the treatment of patients with dementia-related psychosis.

**Contraindications:** LYBALVI is contraindicated in patients who are using opioids or are undergoing acute opioid withdrawal. If LYBALVI is administered with lithium or valproate, refer to the lithium or valproate Prescribing Information for the contraindications for these products.

**Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis,** including stroke, transient ischemia attack, and fatalities. See Boxed Warning above.

**Precipitation of Severe Opioid Withdrawal in Patients who are Physiologically Dependent on Opioids:** LYBALVI can precipitate opioid withdrawal in patients who are dependent on opioids, which can lead to an opioid withdrawal syndrome, sometimes requiring hospitalization. LYBALVI is contraindicated in patients who are using opioids or undergoing acute opioid withdrawal. Prior to initiating LYBALVI, there should be at least a 7-day opioid-free interval from last use of short-acting opioids, and at least a 14-day opioid-free interval from the last use of long-acting opioids. Explain the risks associated with precipitated withdrawal and the importance of giving an accurate account of last opioid use to patients and caregivers.

**Vulnerability to Life-Threatening Opioid Overdose:** Attempting to overcome opioid blockade with high or repeated doses of exogenous opioids could lead to life-threatening or fatal opioid intoxication, particularly if LYBALVI therapy is interrupted or discontinued subjecting the patient to high levels of unopposed opioid agonist as the samidorphan blockade wanes. Inform patients of the potential consequences of trying to overcome the opioid blockade and the serious risks of taking opioids concurrently with LYBALVI or while transitioning off LYBALVI. In emergency situations, if a LYBALVI-treated patient requires opioid treatment as part of anesthesia or analgesia, discontinue LYBALVI. Opioids should be administered by properly trained individual(s) and patient should be continuously monitored in a setting equipped and staffed for cardiopulmonary resuscitation. Patients with a history of chronic opioid use prior to treatment with LYBALVI may have decreased opioid tolerance if LYBALVI therapy is interrupted or discontinued. Advise patients that this decreased tolerance may increase the risk of opioid overdose if opioids are resumed at the previously tolerated dosage.

**Neuroleptic Malignant Syndrome,** 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, intensive symptomatic treatment, and close monitoring.

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

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), a potentially fatal condition reported with exposure to olanzapine, a component of LYBALVI. Symptoms include a cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, and/or lymphadenopathy with systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and/or pericarditis. Discontinue if DRESS is suspected.

Metabolic Changes, including hyperglycemia, diabetes mellitus, dyslipidemia, and weight gain. Hyperglycemia, in some cases extreme and associated with ketoadiposis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Any patient treated with LYBALVI should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required anti-diabetic treatment despite discontinuation of the suspect drug. Measure weight and assess fasting glucose and lipids when initiating LYBALVI and monitor periodically.

Tardive Dyskinesia (TD): Risk of developing TD (a syndrome of potentially irreversible, involuntary, dyskinetic movements) and the likelihood it will become irreversible increases 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 discontinuation. Given these considerations, LYBALVI should be prescribed in a manner that is most likely to reduce the risk of tardive dyskinesia. If signs and symptoms of TD appear, drug discontinuation should be considered.

Orthostatic Hypotension and Syncope: Monitor orthostatic vital signs in patients who are vulnerable to hypotension, patients with known cardiovascular disease, and patients with cerebrovascular disease.

Falls: LYBALVI may cause somnolence, postural hypotension, and motor and sensory instability, which may lead to falls, and consequently, fractures or other injuries. Assess patients for risk when using LYBALVI.

Leukopenia, Neutropenia, and Agranulocytosis (including fatal cases): Perform complete blood counts in patients with a history of a clinically significant low white blood cell (WBC) count or history of leukopenia or neutropenia. Discontinue LYBALVI if clinically significant decline in WBC occurs in the absence of other causative factors.

Dysphagia: Use LYBALVI with caution in patients at risk for aspiration.

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

Potential for Cognitive and Motor Impairment: Because LYBALVI may cause somnolence, impairment judgment, thinking, or motor skills, caution patients about operating hazardous machinery, including motor vehicles, until they are certain that LYBALVI does not affect them adversely.

Body Temperature Dysregulation: Use LYBALVI with caution in patients who may experience conditions that increase core body temperature (e.g., strenuous exercise, extreme heat, dehydration, or concomitant use with anticholinergics).

Anticholinergic (Antimuscarinic) Effects: Olanzapine, a component of LYBALVI, was associated with constipation, dry mouth, and tachycardia. Use LYBALVI with caution with other anticholinergic medications and in patients with urinary retention, prostatic hypertrophy, constipation, paralytic ileus or related conditions. In postmarketing experience, the risk for severe adverse reactions (including fatalities) was increased with concomitant use of anticholinergic medications.

Hyperprolactinemia: LYBALVI elevates prolactin levels. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds.

Risks Associated with Combination Treatment with Lithium or Valproate: If LYBALVI is administered with lithium or valproate, refer to the lithium or valproate Prescribing Information for a description of the risks for these products.

Most common adverse reactions observed in clinical trials were:

- Schizophrenia (LYBALVI): weight increased, somnolence, dry mouth, and headache
- Bipolar I Disorder, Manic or Mixed Episodes (olanzapine): asthenia, dry mouth, constipation, increased appetite, somnolence, dizziness, tremor
- Bipolar I Disorder, Manic or Mixed Episodes, adjunct to Lithium or Valproate (olanzapine): dry mouth, dyspepsia, weight gain, increased appetite, dizziness, back pain, constipation, speech disorder, increased salivation, amnesia, paresthesia

Concomitant Medication: LYBALVI is contraindicated in patients who are using opioids or undergoing acute opioid withdrawal. Concomitant use of LYBALVI is not recommended with strong CYP3A4 inducers, levodopa and dopamine agonists. Reduce dosage of LYBALVI when using with strong CYP1A2 inhibitors. Increase dosage of LYBALVI with CYP1A2 inducers. Use caution with diazepam, alcohol, other CNS acting drugs, or in patients receiving anticholinergic (antimuscarinic) medications. Monitor blood pressure and reduce dosage of antihypertensive drug in accordance with its approved product labeling.

Pregnancy: May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during treatment with LYBALVI. Inform patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to LYBALVI during pregnancy.

Renal Impairment: LYBALVI is not recommended for patients with end-stage renal disease (eGFR of <15 mL/minute/1.73 m²).

To report SUSPECTED ADVERSE REACTIONS, contact Alkermes at 1-888-235-8008 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see the Brief Summary of full Prescribing Information, including Boxed Warning, for LYBALVI on the following pages.
INDICATIONS AND USAGE
LYBALVI is indicated for the treatment of:

- Schizophrenia in adults
- Bipolar I disorder in adults
  - Acute treatment of manic or mixed episodes as monotherapy and as adjunct to lithium or valproate
  - Maintenance monotherapy treatment

CONTRAINDICATIONS
LYBALVI is contraindicated in patients:

- who are using opioids
- who are undergoing acute opioid withdrawal

If LYBALVI is administered with lithium or valproate, refer to the lithium or valproate prescribing information for the contraindications for these products.

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. In placebo-controlled clinical trials of elderly patients with dementia-related psychosis, the incidence of death in dementiapopreated patients was significantly greater than in placebo-treated patients (3.9% vs 1.5%, respectively). Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in the drug-treated patients of 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 0.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. LYBALVI is not approved for the treatment of patients with dementia-related psychosis.

Cerebrovascular Adverse Reactions, Including Stroke in Elderly Patients with Dementia-Related Psychosis: Cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack) including fatalities, were reported in patients in trials of olanzapine in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse reactions in patients treated with olanzapine compared to patients treated with placebo. LYBALVI is not approved for the treatment of patients with dementiap related psychosis.

Precipitation of Severe Opioid Withdrawal in Patients Who Are Physiologically Dependent on Opioids: Samidorphan, an opioid antagonist that is a component of LYBALVI, can precipitate opioid withdrawal in patients who are dependent on opioids, which can lead to an opioid withdrawal syndrome, sometimes requiring hospitalization. Therefore, LYBALVI is contraindicated in patients who are using opioids or undergoing acute opioid withdrawal. Prior to initiating LYBALVI, there should be at least a 7-day opioid-free interval from last use of short-acting opioids, and at least a 14-day opioid-free interval from the last use of long-acting opioids. Explain the risks associated with precipitated withdrawal and the importance of giving an accurate account of last opioid use to patients and caregivers.

Vulnerability to Life-Threatening Opioid Overdose
Risk of Opioid Overdose from Attempts to Overcome Samidorphan Blockade:
LYBALVI contains samidorphan, an opioid antagonist. Attempting to overcome LYBALVI’s opioid blockade with high or repeated doses of exogenous opioids (e.g., because of ineffective analgesia or opioid withdrawal symptoms) could lead to life-threatening or fatal opioid intoxication (e.g., respiratory arrest, circulatory collapse), particularly if LYBALVI therapy is interrupted or discontinued, subjecting the patient to high levels of unopposed opioid agonist as the samidorphan blockade wanes. Inform patients of the potential consequences of trying to overcome the opioid blockade and the serious risks of taking opioids concurrently with LYBALVI or while transitioning off LYBALVI.

In emergency situations, if a LYBALVI-treated patient requires opioid treatment as part of anesthesia or analgesia:

- Discontinue LYBALVI.
- Opioids should be administered by individual(s) trained in the use of anesthetic drugs and the management of the respiratory effects of opioids, specifically the establishment and maintenance of a patent airway and assisted ventilation, and
- Appropriately trained personnel should continuously monitor the patient in a setting equipped and staffed for cardiopulmonary resuscitation.

For recommendations on starting opioids in LYBALVI-treated patients in non-emergent situations, see DRUG INTERACTIONS section.

Risk of Resuming Opioids in Patients with Prior Opioid Use
Patients with a history of chronic opioid use prior to treatment with LYBALVI may have decreased opioid tolerance if LYBALVI therapy is interrupted or discontinued. Advise patients that this decreased tolerance may increase the risk of opioid overdose if opioids are resumed at the previously tolerated dosage.

Neuroleptic Malignant Syndrome: Neuroleptic Malignant Syndrome (NMS), a potentially fatal symptom complex, has been reported in association with administration of antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, deliriun, and autonomic instability. Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

If NMS is suspected, immediately discontinue LYBALVI and provide intensive symptomatic treatment and monitoring.

Drug Reaction with Eosinophilia and Systemic Symptoms: Drug-Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported with exposure to olanzapine, a component of LYBALVI. DRESS may present with a cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, and/or lymphadenopathy with systemic complications such as hepatitis, nephritis, pneumonitis, myocardiut, and/or pericarditis. DRESS is sometimes fatal. Discontinue LYBALVI if DRESS is suspected.

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

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Any patient treated with LYBALVI should be monitored for symptoms of hyperglycemia including polydypsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with LYBALVI should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required anti-diabetic treatment despite discontinuation of the suspect drug. Patients starting treatment with LYBALVI should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment.

Antipsychotics have caused adverse alterations in lipids. Patients starting treatment with LYBALVI should undergo fasting lipid profile testing at the beginning of treatment and periodically during treatment.

Weight gain has been observed with use of antipsychotics. Monitor weight prior to initiating LYBALVI and frequently thereafter.

Tardive Dyskinesia: Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with antipsychotic drugs. The risk appears to be highest among the elderly, especially elderly women, but it is not possible to predict which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible increases with the duration of treatment and the cumulative dose. The syndrome can develop after a relatively brief treatment period, even at low doses. It may also occur after discontinuation of treatment.

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

Given these considerations, LYBALVI should be prescribed in a manner that is most likely to reduce the risk of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients: 1) who suffer from a chronic illness that is known to respond to antipsychotic drugs and 2) for whom alternative, effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, use the lowest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. Periodically reassess the need for continued treatment.

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

Orthostatic Hypotension and Syncope: Atypical antipsychotics cause orthostatic hypotension and syncope. Generally, the risk is greatest during initial dose titration and when increasing the dose. In the 4-week, placebo-controlled study, from analysis of the vital signs data, rates of orthostatic hypotension were less than 2% in LYBALVI- and placebo-, and olanzapine-treated patients. In the 24-week, olanzapine-controlled study, from analysis of the vital signs data, rates of orthostatic hypotension in LYBALVI-treated patients were 3.7%, compared to 0.4% in olanzapine-treated patients.
Monitor orthostatic vital signs in patients who are vulnerable to hypotension (e.g., elderly patients, patients with dehydration, hypovolemia, concomitant treatment with antihypertensive medications or CNS depressants, patients with known cardiovascular disease (history of myocardial infarction, ischemic heart disease, heart failure, or conduction abnormalities), and patients with cerebrovascular disease. LYBALVI has not been evaluated in patients with a recent history of myocardial infarction or unstable cardiovascular disease. Such patients were excluded from the premarketing clinical trials.

**Falls:** Antipsychotics, including LYBALVI, 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 can exacerbate these effects, complete fall risk assessments when initiating antipsychotic treatment and frequently for patients on long-term antipsychotic therapy.

**Leukopenia, Neutropenia, and Agranulocytosis:** Leukopenia and neutropenia have been reported during treatment with antipsychotic agents, including LYBALVI. Agranulocytosis (including fatal cases) has been reported with other agents in this class.

Possible risk factors for leukopenia and neutropenia include pre-existing low white blood cell count (WBC) or absolute neutrophil count (ANC) and history of drug-induced leukopenia or neutropenia. In patients with a pre-existing low WBC or ANC or a history of drug-induced leukopenia or neutropenia, perform a complete blood count (CBC) frequently during the first few months of therapy. In such patients, consider discontinuation of LYBALVI at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treat promptly if such symptoms or signs occur. Discontinue LYBALVI in patients with severe neutropenia (absolute neutrophil count <1000/mm³) and follow their WBC until recovery.

**Dysphagia:** Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Antipsychotic drugs, including LYBALVI, should be used cautiously in patients at risk for aspiration.

**Seizures:** Like other antipsychotic drugs, LYBALVI may cause seizures. This risk is greatest in patients with a history of seizures or with conditions that lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in older patients.

**Potential for Cognitive and Motor Impairment:** LYBALVI, like other antipsychotics, may cause somnolence and has the potential to impair judgment, thinking, or motor skills. In a LYBALVI placebo-controlled study, somnolence occurred in 9% of LYBALVI-treated patients compared to 2.2% in patients treated with placebo.

Patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that LYBALVI therapy does not affect them adversely.

**Body Temperature Dysregulation:** Atypical antipsychotics may disrupt the body’s ability to regulate core body temperature. Strenuous exercise, exposure to extreme heat, dehydration, and anticholinergic medications may contribute to an elevation in core body temperature; use LYBALVI with caution in patients who may experience these conditions.

**Anticholinergic (Antimuscarinic) Effects:** Olanzapine, a component of LYBALVI, exhibits in vitro muscarinic receptor affinity. In premarketing clinical trials with oral olanzapine, olanzapine was associated with constipation, dry mouth, and tachycardia, all adverse reactions possibly related to cholinergic antagonism. Such adverse reactions were not often the basis for discontinuations, but LYBALVI should be used with caution in patients with a current diagnosis or prior history of urinary retention, clinically significant prostatic hypertrophy, constipation, or a history of paralytic ileus or related conditions. In postmarketing experience, the risk for severe adverse reactions (including fatalities) was increased with concomitant use of anticholinergic medications.

**Hyperprolactinemia:** As with other drugs that antagonize dopamine D₂ receptors, olanzapine, a component of LYBALVI, elevates prolactin levels, and the elevation can persist during chronic administration. Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects.

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent in vitro, a factor of potential importance if the prescription of these drugs is considered in a patient with previously-detected breast cancer. As is common with compounds which increase prolactin release, an increase in mammary gland neoplasia was observed in the olanzapine carcinogenicity studies conducted in mice and rats. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans, but the available evidence is too limited to be conclusive.

In the 4-week placebo-controlled trial, shifts from normal to high prolactin values (>30 ng/mL for females; >20 ng/mL for males) occurred in 41.4% of females and 32.9% of males treated with LYBALVI, in 56.1% of females and 37.1% of males treated with olanzapine, and in 10% of females and 4.8% of males treated with placebo.

In the 24-week, olanzapine-controlled study, shifts from normal to high prolactin values occurred in 32.9% of females and 22.5% of males treated with LYBALVI, and in 41.7% of females and 28.5% of males treated with olanzapine.

**Risks Associated with Combination Treatment with Lithium or Valproate:** If LYBALVI is administered with lithium or valproate, refer to the lithium or valproate Precribing Information for a description of the risks for these products including, but not limited to, the warnings and precautions for lithium or valproate.

**ADVERSE REACTIONS**

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

**Adverse Reactions in Patients with Schizophrenia:**

**Patient Exposure**

The safety of LYBALVI was evaluated in 1262 patients (18 to 67 years of age) diagnosed with schizophrenia in four double-blind, controlled studies and three long-term safety extension studies of up to 3 years of duration. This experience corresponds to approximately 910 person-years. In these studies, there were a total of 663 patients exposed to LYBALVI for at least 6 months, and 386 patients for at least one year.

**Adverse Reactions in the Short-Term (4 week) Placebo-Controlled Trial in Adults with Schizophrenia**

The most common adverse reactions (incidence of at least 5%) of patients exposed to LYBALVI and greater than twice the rate of placebo) are weight increased, somnolence, dry mouth, and headache.

Adverse reactions associated with the use of LYBALVI (incidence of 2% or greater and greater than in placebo-treated patients) are shown in Table 1.

### Table 1: Adverse Reactions Reported in ≥2% of LYBALVI-Treated Patients and Greater than Placebo in a 4-Week Schizophrenia Trial

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo (N=153)</th>
<th>LYBALVI (10 mg/10 mg, 20 mg/10 mg) (N=134)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight increased</td>
<td>3 (2%)</td>
<td>19 (13%)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>2 (1%)</td>
<td>9 (6%)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>1 (0.6%)</td>
<td>7 (5%)</td>
</tr>
<tr>
<td>Headache</td>
<td>3 (2%)</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Blood insulin increased</td>
<td>1 (0.7%)</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>Sedation</td>
<td>0 (0%)</td>
<td>2 (1.5%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (0.7%)</td>
<td>2 (1.5%)</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>0 (0%)</td>
<td>2 (1.5%)</td>
</tr>
</tbody>
</table>

Adverse reactions that led to discontinuation in LYBALVI-treated patients in the short-term placebo-controlled trial in adults with schizophrenia include schizophrenia (1%) and abnormal liver function tests (1%).

**Adverse Reactions in the Long-Term (24-week), Active-Controlled Trial in Adults with Schizophrenia**

In the 24-week, olanzapine-controlled trial in patients with stable schizophrenia, adverse reactions associated with the use of LYBALVI (incidence of 2% or greater) include: weight increased (25%), somnolence (21%), dry mouth (13%), increased appetite (11%), waist circumference increased (6%), blood creatinine phosphokinase increased (5%), headache (4%), lethargy (4%), sedation (4%), akathisia (3%), alanine aminotransferase increased (3%), aspartate aminotransferase increased (3%), constipation (3%), dizziness (3%), fatigue (3%), nausea (3%), blood pressure increased (3%), neutrophil count decreased (3%), blood insulin increased (2%), weight decreased (2%), and dyslipidemia (2%).

Adverse reactions that led to LYBALVI treatment discontinuation in more than one patient include somnolence (2%), weight increased (2%), neutropenia (2%), glucose stabilized hemoglobin increased (1%), schizophrenia (1%), and liver function test abnormal (1%).

**Hypoglycemia:** Mean increases in blood glucose have been observed in patients treated (median exposure of 9.2 months) with olanzapine in phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE). The mean increase of serum glucose (fasting and nonfasting samples) from baseline to the average of
the 2 highest serum concentrations was 15.0 mg/dL. Hyperglycemia, as defined by fasting glucose ≥126 mg/dL, has been observed in patients treated with LYBALVI. In the 4-week placebo-controlled trial in adult patients with schizophrenia, shifts in fasting glucose from normal to high occurred in 4% of patients treated with LYBALVI, 1% of patients treated with olanzapine, and no patients treated with placebo.

In the 24-week olanzapine-controlled trial, patients treated with LYBALVI were more likely to experience abnormal shifts in glycemic parameters than patients treated with olanzapine (Table 2).

### Table 2: Changes in Glycemic Parameters in a 24-Week Trial of Patients with Schizophrenia

<table>
<thead>
<tr>
<th>Proportion of Patients with Shifts, % (n/N)*</th>
<th>LYBALVI</th>
<th>Olanzapine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose Normal to High (≥100 mg/dL to ≥126 mg/dL)</td>
<td>12 (26/223)</td>
<td>8 (19/219)</td>
</tr>
<tr>
<td>Impaired (≥100 mg/dL and &lt;126 mg/dL) to High (≥126 mg/dL)</td>
<td>24 (9/38)</td>
<td>11 (5/47)</td>
</tr>
<tr>
<td>Increase ≥10 mg/dL</td>
<td>66 (174/265)</td>
<td>57 (154/270)</td>
</tr>
<tr>
<td>Hemoglobin A1c Normal (≤5.7%) to Impaired (≥5.7% and &lt;6.5%)</td>
<td>42 (86/204)</td>
<td>35 (68/197)</td>
</tr>
<tr>
<td>Normal to High (≥5.7% and ≤6.5%)</td>
<td>0.5 (1/204)</td>
<td>1.5 (3/197)</td>
</tr>
<tr>
<td>Impaired (≥5.7% and &lt;6.5%) to High (≥6.5%)</td>
<td>9.5 (6/63)</td>
<td>9.2 (7/76)</td>
</tr>
</tbody>
</table>

* n: number of patients with reported abnormal shifts; N: number of patients who had assessments at both baseline and endpoint for mean change, or normal at baseline and at least 1 post-baseline assessment for shift.

Dyslipidemia: In the 4-week, placebo-controlled trial in adult patients with schizophrenia, shifts in fasting triglycerides from normal to high occurred in 14% of patients treated with LYBALVI and 4% of patients treated with placebo.

In the 24-week olanzapine-controlled study, mean changes in fasting total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides were similar in patients treated with LYBALVI and in patients treated with olanzapine.

Weight Gain: In the 4-week placebo-controlled study in adult patients with schizophrenia, mean changes in weight, and proportion of patients with ≥7% weight increase, were greater in patients treated with LYBALVI and olanzapine than in patients on placebo. In that study, mean weight gain was 3.0 kg in patients treated with LYBALVI, 2.4 kg in patients treated with olanzapine, and 0.2 kg in patients treated with placebo. The proportion of patients with ≥7% weight increase was 26% in patients treated with LYBALVI, 20% in patients treated with olanzapine, and 5% in patients treated with placebo.

In the 24-week trial, LYBALVI-treated patients gained on average 4.2% of baseline body weight. The proportion of patients treated with LYBALVI with ≥10% body weight gain was 17.8%.

Extrapyramidal Symptoms: In the 4-week placebo-controlled trial in adult patients with schizophrenia, patients were assessed using the Simpson-Angus Rating Scale (SAS) for extrapyramidal symptoms (EPS) (total score ranges from 1 to 14), the Barnes Akathisia Rating Scale (BARS) for akathisia (total score ranges from 0 to 14), and the Abnormal Involuntary Movement Scale (AIMS) for dyskinesias (total score ranges from 0 to 28). The mean changes from baseline to last study visit for the BAS, SARS, and AIMS was similar in LYBALVI-treated patients and in placebo-treated patients. The mean changes for LYBALVI- vs placebo-treated patients were 0.00 vs -0.2 for AIMS, 0.0 vs -0.1 for BARS, and 0.0 vs -0.3 for SAS, respectively.

The rate of Parkinsonism (SAS total score ≥3) was lower in patients treated with LYBALVI (4%) compared to those on placebo (1%). The rates of akathisia (BARS global clinical assessment score ≥2) and dyskinesia (AIMS score ≥3) on any of the first 7 items, or a score ≥2 on two or more of any of the first 7 items were similar in patients treated with LYBALVI and in those on placebo. Rates of akathisia were 6.0% and 8.2% in patients treated with LYBALVI and placebo, respectively, and the rate of dyskinesia was 1.5% both in LYBALVI-treated and in placebo-treated patients.

The frequency of reported adverse reactions related to extrapyramidal symptoms, including akathisia, restlessness, muscle spasms, bradykinesia, tremor, extrapyramidal disorder, and Parkinsonism was 2% both in LYBALVI-treated and in placebo-treated patients.

In the 24-week active-controlled trial, the mean change from baseline to the last visit for the SAS, BARS, and AIMS was similar in LYBALVI-treated patients and in those treated with the active control. Extrapyramidal adverse reactions, including parkinsonism, akathisia, and dyskinesia, had a similar incidence in LYBALVI-treated patients and in those treated with the active control: any extrapyramidal symptom was 6%, akathisia was 3%.

**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 high potency and at higher doses of first-generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

**Adverse Reactions in Patients with Bipolar Disorder:** The safety of LYBALVI for the treatment of bipolar I disorder (mixed or manic) monotherapy and adjunct to lithium or valproate relies on information from adequate and well-controlled studies of olanzapine tablets in bipolar I disorder.

The most common adverse reactions (incidence of at least 5% of patients exposed to olanzapine and greater than or equal to twice the rate of placebo) from short-term trials of olanzapine (manic or mixed episodes) are somnolence, dry mouth, dizziness, asthenia, constipation, dyspepsia, increased appetite, and tremor.

The most common adverse reactions (incidence of at least 5% of patients exposed to olanzapine greater than or equal to twice the rate of placebo) from short-term trials of olanzapine as adjunct to lithium or valproate (manic or mixed episodes) are dry mouth, weight gain, increased appetite, dizziness, back pain, constipation, speech disorder, increased salivation, anemia, paresthesia.

**Postmarketing Experience:** The following adverse reactions have been identified during post-approval use of olanzapine. Because these reactions are reported voluntarily from a population of uncertain size, it is difficult to reliably estimate their frequency or evaluate a causal relationship to drug exposure.

- allergic reactions (e.g., anaphylactoid reaction, angioedema, pruritis or urticaria)
- cholestatic or mixed liver injury, hepatitis, jaundice
- diabetic coma, diabetic ketoacidosis
- discontinuation reaction (diaphoresis, nausea or vomiting)
- Drug reaction with eosinophilia and systemic symptoms (DRESS)
- hyperlipidemia (random cholesterol levels ≥300 mg/dl and random triglyceride levels ≥500 mg/dl have been reported)
- neutropenia
- pancreatitis
- priapism
- rash
- restless legs syndrome
- rhabdomyolysis
- salivary hypersecretion
- stuttering
- venous thromboembolic events (including pulmonary embolism and deep venous thrombosis)

1 Stuttering was only studied in oral and long-acting injection (LAI) formulations.

**DRUG INTERACTIONS**

**Effects of Other Drugs on LYBALVI:** Table 3 describes clinically significant drug interactions where the concomitant use of other drugs affects LYBALVI.

### Table 3: Effects of Other Drugs on LYBALVI

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Lybalvi Contraindicated</th>
<th>Lybalvi Dose Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong CYP3A4 Inducer</td>
<td>Coadministration of LYBALVI with a strong CYP3A4 inducer decreases AUC, of olanzapine and samidorphan which may reduce LYBALVI efficacy.</td>
<td>Prevention or Management: Concomitant use of LYBALVI with strong CYP3A4 inducers is not recommended.</td>
</tr>
<tr>
<td>CYP3A4 Inhibitor</td>
<td>Concomitant use of LYBALVI with a strong CYP3A4 inhibitor increases olanzapine AUC and Cmax, which may increase risk of LYBALVI adverse reactions.</td>
<td>Prevention or Management: Consider reducing the dosage of the olanzapine component in LYBALVI when used concomitantly with strong CYP3A4 inhibitors.</td>
</tr>
<tr>
<td>CYP1A2 Inhibitor</td>
<td>Concomitant use of LYBALVI with CYP1A2 inhibitors decreases olanzapine exposure, which may reduce LYBALVI efficacy.</td>
<td><strong>CYP1A2 Inhibitor</strong></td>
</tr>
</tbody>
</table>

- **CYP1A2 Inhibitor**
Pregnancy may be less effective or ineffective shortly after LYBALVI discontinuation because given that LYBALVI contains samidorphan, an opioid antagonist, opioid treatment (e.g., for analgesia during or after an elective surgical procedure) could be monitored for excess sedation, irritability, poor feeding and extrapyramidal symptoms (tremors and abnormal muscle movements). Infants exposed to LYBALVI should be monitored for adverse effects on embryofetal development when the presence of samidorphan.

**Table 3: Effects of Other Drugs on LYBALVI (cont’d)**

<table>
<thead>
<tr>
<th>Prevention or Management</th>
<th>Diazepam, Alcohol and CNS Acting Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Implication</td>
<td>Concomitant use of diazepam, alcohol, or other CNS acting drugs with LYBALVI may potentiate orthostatic hypotension observed with olanzapine.</td>
</tr>
<tr>
<td>Prevention or Management</td>
<td>LYBALVI should be used with caution in patients receiving concomitantly diazepam or other CNS acting drugs, or using alcohol.</td>
</tr>
</tbody>
</table>

**Anticholinergic Drugs**

<table>
<thead>
<tr>
<th>Clinical Implication</th>
<th>Concomitant treatment with olanzapine and other drugs with anticholinergic activity can increase the risk for severe gastrointestinal adverse reactions related to hypomotility.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevention or Management</td>
<td>Consider increasing the dosage of the olanzapine component in LYBALVI when used concomitantly with CYP1A2 inducers.</td>
</tr>
</tbody>
</table>

**Effects of LYBALVI on Other Drugs**

Table 4 describes clinically significant drug interactions where concomitant use of LYBALVI affects other drugs.

**Table 4: Effects of LYBALVI on Other Drugs**

<table>
<thead>
<tr>
<th>Prevention or Management</th>
<th>Antihypertensive Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Implication</td>
<td>LYBALVI may enhance the effects of certain antihypertensive agents.</td>
</tr>
<tr>
<td>Prevention or Management</td>
<td>Monitor blood pressure and reduce dosage of antihypertensive drug in accordance with its approved product labeling.</td>
</tr>
</tbody>
</table>

**Levodopa and Dopamine Agonists**

<table>
<thead>
<tr>
<th>Clinical Implication</th>
<th>LYBALVI may antagonize the effects of levodopa and dopamine agonists.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevention or Management</td>
<td>Concomitant use of LYBALVI is not recommended with levodopa and dopamine agonists.</td>
</tr>
</tbody>
</table>

**Opioids:** LYBALVI is contraindicated in patients who are using opioids or undergoing acute opioid withdrawal.

LYBALVI increases the risk of precipitating acute opioid withdrawal in patients who are dependent on opioids. Prior to initiating LYBALVI, there should be at least a 7-day opioid-free interval from the last use of short-acting opioids, and at least a 14-day opioid-free interval from the last use of long-acting opioids. In emergency situations, if a LYBALVI-treated patient requires opioid treatment for anesthesia or analgesia, discontinue LYBALVI. The opioid should be administered by properly trained individual(s), and the patient should be properly monitored in a setting equipped and staffed for cardiopulmonary resuscitation.

In non-emergency situations, if a LYBALVI-treated patient is expected to require opioid treatment (e.g., for analgesia during or after an elective surgical procedure) discontinue LYBALVI at least 5 days before opioid treatment and start olanzapine or another antipsychotic, if needed. Given that LYBALVI contains samidorphan, an opioid antagonist, opioid treatment may be less effective or ineffective shortly after LYBALVI discontinuation because of the presence of samidorphan.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Prevention or Management:** Consider increasing the dosage of the olanzapine component in LYBALVI when used concomitantly with CYP1A2 inducers.

**Clinical Implication:** Opioids: LYBALVI is contraindicated in patients who are using opioids or undergoing acute opioid withdrawal. LYBALVI increases the risk of precipitating acute opioid withdrawal in patients who are dependent on opioids. Prior to initiating LYBALVI, there should be at least a 7-day opioid-free interval from the last use of short-acting opioids, and at least a 14-day opioid-free interval from the last use of long-acting opioids. In emergency situations, if a LYBALVI-treated patient requires opioid treatment for anesthesia or analgesia, discontinue LYBALVI. The opioid should be administered by properly trained individual(s), and the patient should be properly monitored in a setting equipped and staffed for cardiopulmonary resuscitation.

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**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

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**Clinical Implication:** Opioids: LYBALVI is contraindicated in patients who are using opioids or undergoing acute opioid withdrawal. LYBALVI increases the risk of precipitating acute opioid withdrawal in patients who are dependent on opioids. Prior to initiating LYBALVI, there should be at least a 7-day opioid-free interval from the last use of short-acting opioids, and at least a 14-day opioid-free interval from the last use of long-acting opioids. In emergency situations, if a LYBALVI-treated patient requires opioid treatment for anesthesia or analgesia, discontinue LYBALVI. The opioid should be administered by properly trained individual(s), and the patient should be properly monitored in a setting equipped and staffed for cardiopulmonary resuscitation.

In non-emergency situations, if a LYBALVI-treated patient is expected to require opioid treatment (e.g., for analgesia during or after an elective surgical procedure) discontinue LYBALVI at least 5 days before opioid treatment and start olanzapine or another antipsychotic, if needed. Given that LYBALVI contains samidorphan, an opioid antagonist, opioid treatment may be less effective or ineffective shortly after LYBALVI discontinuation because of the presence of samidorphan.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Prevention or Management:** Consider increasing the dosage of the olanzapine component in LYBALVI when used concomitantly with CYP1A2 inducers.

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In non-emergency situations, if a LYBALVI-treated patient is expected to require opioid treatment (e.g., for analgesia during or after an elective surgical procedure) discontinue LYBALVI at least 5 days before opioid treatment and start olanzapine or another antipsychotic, if needed. Given that LYBALVI contains samidorphan, an opioid antagonist, opioid treatment may be less effective or ineffective shortly after LYBALVI discontinuation because of the presence of samidorphan.
Olanzapine

Olanzapine was orally administered to pregnant rats and rabbits during the period of organogenesis at doses of 25, 100, and 300 mg/kg/day, which are approximately 29 and 742 times the MRHD of 10 mg/day based on AUC. Samidorphan was associated with an increased incidence of skeletal variations (unossified sternabrae and bent ribs) at maternally toxic doses of ≥100 mg/kg/day, and skeletal malformations (bent or misshapen forelimbs, hindlimbs, and/or scapula) at 300 mg/kg/day which are >2 and 742 times the MRHD based on AUC, respectively. The NOAEL for embryofetal development is 25 mg/kg/day, which is approximately 29 times the MRHD based on AUC.

Samidorphan was orally administered to pregnant rats during the period of organogenesis at doses of 10, 30, and 90 mg/kg/day, which are up to approximately 143 times the MRHD based on AUC.

Samidorphan was orally administered to pregnant rats during pregnancy and lactation at doses of 10, 30, or 100 mg/kg/day, which are approximately 7 to 188 times the MRHD based on AUC. Reduced pup survival, lower birth weights, and decreased pup body weight gains were observed at 100 mg/kg/day, which is 188 times the MRHD based on AUC. The NOAEL of 30 mg/kg/day is approximately 36 times the MRHD based on AUC. There were no adverse effects on pup development, landmarks, learning, memory, reflexes, or fertility.

Lactation

Risk Summary: Olanzapine is present in human milk. There are reports of excess sedation, irritability, poor feeding and extrapyramidal symptoms (tremors and abnormal muscle movements) in infants exposed to olanzapine through breast milk. There is no information on the effects of olanzapine on milk production. There are no data on the presence of samidorphan or the combination of olanzapine and samidorphan in human milk, the effects on the breastfed infant or the effects on milk production. When samidorphan was administered to lactating rats, samidorphan and a metabolite were detected in the plasma of nursing pups, likely due to the presence of samidorphan in milk. Infants exposed to LYBALVI should be monitored for excess sedation, irritability, poor feeding and extrapyramidal symptoms (tremors and abnormal muscle movements).

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

Females and Males of Reproductive Potential

Infertility

Females

Based on the pharmacologic action of olanzapine (D2 antagonism), treatment with LYBALVI may result in an increase in serum prolactin levels, which may lead to a reversible reduction in fertility in females of reproductive potential.

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

Geriatric Use: Clinical studies of LYBALVI did not include sufficient numbers of patients 65 years of age and older to determine whether they responded differently than younger adult patients.

Olanzapine: Of the 2,500 patients in premarketing clinical studies with orally administered olanzapine, 11% (263) were 65 years of age or over. Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. LYBALVI is not approved for the treatment of patients with dementia-related psychosis.

Studies in elderly patients with dementia-related psychosis have suggested that there may be a different tolerability profile in this population compared to younger patients with schizophrenia. Elderly patients with dementia-related psychosis treated with olanzapine are at an increased risk of death compared to placebo.

• In placebo-controlled studies of olanzapine in elderly patients with dementia-related psychosis, there was a higher incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack) in patients treated with olanzapine, compared to patients treated with placebo.

• In five placebo-controlled studies of olanzapine in elderly patients with dementia-related psychosis (n=1,184), the following adverse reactions were reported in olanzapine-treated patients at an incidence of at least 2% and significantly greater than in placebo-treated patients: falls, somnolence, peripheral edema, abnormal gait, urinary incontinence, lethargy, increased weight, asthma, pneumonia, pulmonary disease, hypotension, and visual hallucinations. The rate of discontinuation due to adverse reactions was greater with olanzapine than with placebo (13% vs 7%).

Consider a lower dosage of the olanzapine component of LYBALVI in geriatric patients who may have decreased clearance or an exaggerated pharmacodynamic response to olanzapine (e.g., oversedation).

Hepatic Impairment: Olanzapine and samidorphan plasma exposures were found to be higher in subjects with moderate hepatic impairment than in subjects with normal hepatic function. The effect of severe hepatic impairment was not studied. The higher plasma exposure in patients with moderate hepatic impairment was not expected to be clinically relevant. No dose adjustment of LYBALVI is needed in patients with hepatic impairment.

Renal Impairment: Plasma exposure to olanzapine and samidorphan was higher in patients with severe renal impairment compared to those with normal renal function. No dose adjustment of LYBALVI is needed in patients with mild (eGFR 60 to 89 mL/minute/1.73 m²), moderate (eGFR 30 to 59 mL/minute/1.73 m²), or severe renal impairment (eGFR 15 to 29 mL/minute/1.73 m²).

The effect of LYBALVI in patients with end-stage renal disorder was not studied. LYBALVI is not recommended for patients with end-stage renal disorder (eGFR of <15 mL/minute/1.73 m²).

OVERDOSAGE

Human Experience: There is limited clinical experience with overdose with LYBALVI. In premarketing clinical trials of LYBALVI involving 861 patients, overdose of LYBALVI was identified in 7 patients. This included 4 patients with accidental overdose, 2 with intentional overdose, and 1 due to a medication administration error. None of the reported overdoses was associated with a fatal outcome. There was a reported ingestion of 11 tablets of LYBALVI 10 mg/10 mg (5.5 times and 11 times the maximum recommended daily dosage of the olanzapine and samidorphan components of LYBALVI, respectively). The patient was found unresponsive and admitted to the hospital. Medical treatment included fluids, electrolytes, a diuretic, and a detoxificant; the patient stabilized within 2 days.

In postmarketing reports of overdose with olanzapine, a component of LYBALVI, symptoms included agitation/aggressiveness, dysarthria, tachycardia, various extrapyramidal symptoms, and reduced level of consciousness ranging from sedation to coma. Less commonly reported symptoms include: aspiration, convulsion, cardiorespiratory arrest, cardiac arrhythmia (e.g., ventricular tachycardia and 1 patient experiencing sinus pause with spontaneous resumption of normal rhythm), delirium, possible neuroleptic malignant syndrome, respiratory depression/arrest, convulsion, hypertension, and hypotension. In 1 case of death, the amount of acutely ingested olanzapine was reported to be possibly as low as 450 mg; however, in another case, a patient was reported to survive an acute olanzapine ingestion of approximately 2,000 mg.

Management of Overdose: No specific antidotes for LYBALVI 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) for additional overdose management recommendations.

To report SUSPECTED ADVERSE REACTIONS, contact Alkermes, Inc. at 1-888-235-8008 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

This Brief Summary is based on LYBALVI full Prescribing Information (revised: May 2021).

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Challenges and Opportunities Beyond COVID-19

Milton L. Wainberg, MD

The COVID-19 pandemic has had a devastating impact on economies, social structures, and health systems, and it has disproportionately affected low- and middle-income countries (LMICs) as well as low-resourced, disadvantaged settings in high-income countries (HICs). Even before COVID-19, the world confronted substantial challenges in meeting demands for mental and substance use disorder (MSD) care, particularly in low-resource settings. Now, increases in affective symptoms, substance use, suicidality, and cognitive dysfunction have been linked to COVID-19 and its social consequences. Compared with other acute health events, adults have at least twice the risk of receiving a new MSD diagnosis after COVID-19 diagnosis. In turn, psychiatric history is an independent risk factor for COVID-19 infection, and COVID-19’s impact is worse among individuals with MSDs, possibly related to similar inflammatory processes in COVID-19 and psychiatric disorders. This article summarizes the challenges of addressing—and the opportunities to address—the resulting growing global MSD treatment gap.

COVID-19 and the Social Determinants of MSD

Social determinants of MSD that drive global inequalities include poverty, unemployment, stigma and discrimination, lower access to health care and digital infrastructures, and gender, all of which have been exacerbated during the pandemic. COVID-19 has resulted in greater sex differences in MSD prevalence, with women’s mental health likely to be affected more by the pandemic’s social and economic consequences. Stigma toward mental illness is among the most important determinants of MSD. MSD-associated stigma influences policies, research funding, and resource allocation for services. It can have a deleterious effect on providers’ training and intentions to treat patients with MSDs. Low levels of knowledge about MSDs and prejudice and discrimination against people with MSDs serve to delay or prevent access to treatment. Not surprisingly, most of the research on interventions to reduce or prevent MSD stigma and discrimination has taken place in HICs.

COVID-19 and MSD Disparities

In HICs, disenfranchised and minority populations (eg, African Americans, Latinx, impoverished rural populations, migrants, gender minorities in the United States) face MSD disparities that have increased during the pandemic. The impact is even worse in LMICs, where the MSD treatment gap was already vast with 75% to 85% of populations (vs 35% to 50% in HICs) having no access to MSD care. People with MSD experience poor physical health and have an average life expectancy 15 to 25 years shorter than that of the general population. In the Global Burden of Diseases, Injuries, and Risk Factors Study, MSDs were the leading causes of global health-related burden before 2020 across both sexes, the entire lifespan, and world regions. Despite evidence-based interventions (EBIs; eg, short-term psychotherapy treatments, medications) that reduce MSD impact, there has been no reduction in global MSD prevalence since 1990. Unfortunately, EBI scale-up has not been a global priority. Because mental health systems in most countries are underresourced, poorly coordinated, and without supporting policies, access to quality MSD care is limited, especially in LMICs, which is where 90% of the global population resides.

The Global MSD Research Gap Challenge

This gap is among the most important challenges faced by LMICs in implementing MSD EBIs. The Table depicts the science-, health system-, and context-level factors necessary for sustainable scale-up of EBIs. MSD epidemiology, validated measures, and efficacy studies are advanced in HICs, but below average in LMICs. However, the more complex research studies addressing effectiveness and implementation, which are necessary to bridge the research-to-practice gap, are almost as scarce in HICs as in LMICs and they tend to address mostly depression. Few effectiveness and implementation studies address more than 1 disorder at a time. Only 1 addresses all MSDs: an effectiveness-implementation scale-up study in 20 districts and 80 clinics in Mozambique.

The Vast Global Research-to-Practice Gap Challenge

Only half of evidence-based clinical innovations make it into routine delivery in real-world community and clinical settings in HICs—and even fewer do in LMICs. Research through which MSD EBIs are developed and tested typically uses research psychologists to deliver EBIs for single disorders in well-controlled sites. Yet, in the less-resourced and more complex settings in which EBIs actually must be delivered for population impact, clinical personnel may not be as highly trained and supervised, and patients tend to have multiple psychiatric comorbidities and do not receive incentives for participation. Furthermore, because researchers disseminate their work through traditional academic conferences and publications, MSD EBIs are seldom implemented by underresourced public health systems.

Dissemination and implementation science addresses this research-to-practice gap by tackling multilevel contextual barriers and facilitators that influence adoption of EBIs in diverse real-world clinical and community settings and by testing strategies that facilitate EBI implementation. However, the health research continuum process (Figure 1) to achieve intervention implementation is slow and expensive. Furthermore, it typically is undertaken for single MSDs rather than the more typical MSD comorbidities. Thus, the health research continuum, while rigorous, is not the most efficient process for addressing the urgent health care needs faced by HIC low-resource settings and LMICs, particularly in the context of COVID-19—a case, perhaps, in which “perfection is the enemy of progress.” Perhaps the National Institutes of Health Clinical and Translational Science...
MSD specialists are available. Screening for all model using task-shifting in rural clinics where no health workers (CHWs) within primary or community care model has gained momentum in more intensive and expensive treatment by MSD specialists—an effective approach to addressing MSD workforce challenges, strengthening health systems, and increasing MSD care access.

By shifting service delivery for less complex cases to lay providers, MSD specialists can focus on more complex cases in a stepped-care model, in which quality and efficiency of care delivery improve as resources are distributed according to illness severity and need. First-line treatment is provided by trained, task-shifted lay personnel who screen for MSDs and offer EBIs for less severe cases within primary or community care as well as for rehabilitation for people with chronic mental illness. In second-line treatment, integration of depression care into primary care (ie, collaborative care) addresses the needs of more symptomatic patients for antidepressant medication. More intensive and expensive treatment by MSD specialists is then reserved for complex cases. The collaborative care model has gained momentum in HICs, while task-shifting with lay community health workers (CHWs) within primary or community care has been used in LMICs. Like many other studies in LMICs, PRIDE-Mozambique combines a stepped-care model using task-shifting in rural clinics where no MSD specialists are available. Screening for all MSDs in the community is not easy, when CHWs already are charged with addressing multiple health issues (eg, HIV, pregnancy, malaria, tuberculosis, parasitosis, diarrhea). To address this challenge, the US-Mozambique collaboration developed and validated an ultrabrief 3-step screening, triaging, and treatment digital tool—the Electronic Mental Wellness Tool (E-mwTool; Figure 2).

As is customary, in the first step, a CHW gathers household members’ health information from a main household informant. By asking 3 questions about each member, the CHW can identify presence of any MSD with 73% sensitivity. Second, the same 3 items are repeated with the identified member. With 94% sensitivity, CHWs can identify presence of any MSD. Third, for individuals screening positive, 9 more items are used to identify diagnostic categories (eg, severe mental disorders, common mental disorders, substance use disorders, suicide risk) with good specificity, allowing for triage to appropriate EBIs. E-mwTool is being validated in HICs and other LMICs, and added assessment of social determinants of MSD will enable even more specific interventions.

Education and Training Challenges

Task-shifting, stepped care, collaborative care, and community-based care for MSD require strengthening MSD training for all health care providers, including CHWs, to create equitable MSD care access. In addition to increasing knowledge about treating MSDs and addressing provider stigma, health and MSD professional education and training must incorporate both public health and MSD perspectives to go beyond a focus on individual care, which can generate disparities and inequities.

Context-Level Challenges

Services funding, development assistance, and policies that guarantee MSD parity with other health problems are basic for reducing treatment gaps across settings. HICs spend between 5% to 10% of their health budget on MSD. Upper middle-income countries spend about 3%, LMICs about 2%, and low-income countries less than 1%. Consequently, in LMICs, public health system options for psychiatric medications are few. International development support dedicated to MSD is 0.3% of all development assistance for health; it is about 150 times lower than for HIV and 50 times lower than for tuberculosis and malaria.

Most LMICs lack MSD service-related policies, and those that are available do not address the treatment gap. For example, many LMICs only allow MSD specialists to prescribe psychiatric medications; this guarantees virtually no access to psychotherapeutic medications, given the limited numbers of MSD specialists. HICs fare better, but policies still are insufficient to guarantee appropriate access to MSD care, even for those with health insurance. Use of information and communication technologies in MSD services is a novel approach that can overcome delivery barriers. Although this is a growing area of research in HICs, very few studies (eg, PRIDE) take place in LMICs. COVID-19 has led to an exponentially increased use of telehealth to address social distancing guidelines. However, in spite of its health and MSD care benefits for populations that have access to digital tools, telehealth’s use beyond the pandemic may be limited by policies, legislation, and health insurance reimbursements. Low digital-resource settings in HICs and LMICs are unable to use this option without the support of funding, policies, and infrastructure.

Concluding Thoughts

The COVID-19 pandemic has increased urgency for governments and policy makers to strengthen their MSD systems and integrate an MSD response that addresses social determinants of MSDs within their COVID-19 recovery plan. So far, mental health has received an inadequate proportion of health funding in HIC low-resource settings and in LMICs relative to its burden. The COVID-19 pandemic has worsened social determinants of health, and the resulting increased prevalence of MSDs has worsened the global MSD treatment gap. Nevertheless, recognition of the pandemic’s impact on MSDs creates a unique opportunity to work across sectors to increase MSD prevention as well as treatment funding, research, and implementation.

Mental health must be integrated into the global COVID 19 response, with the ability to build capacity for researchers, clinicians, funders, and policy makers to overcome barriers and challenges. Global MSD research must link with policy-making so that EBIs and programs are sustainably adopted and scaled-up within a country’s existing health, educational, and other public systems. HICs and LMICs must transform health provider...
training to incorporate a public health lens and to counter stigma and discrimination. Ministries of health must generate policy for scale-up of stepped-care and community MSD care using EBIs, strengthening existing mental health systems to tackle the pandemic.

Dr Wainberg is a professor of clinical psychiatry at Columbia University and New York State Psychiatric Institute; director of the Mental Health Equity Center at Columbia University/New York State Psychiatric Institute; director of the National Institute of Mental Health (NIMH)-funded Columbia University Global Mental Health Implementation Science T32-Post Doctoral Fellowship, NIMH/Fogarty International-funded Portuguese-speaking African countries Mental Health Implementation Research Training Program; and co-director of the NIMH/Fogarty International-funded Capacity development in HIV and MEntal health Research in Asia (CHIMERA). He is also an founding chair of the Caucus of Global Mental Health and Psychiatry of the American Psychiatric Association, and medical director of the Columbia University HIV Mental Health Training Project.

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Current Health Care System Cannot Survive Aging Population

John M. Ciccone, MD

The United States has the second largest oldest population in the world. By 2050, 21.4% of our population will be 65 years or older. Heart disease and stroke are the leading causes of death in the US population and account for one-third of deaths in the United States annually. The cost is staggering, with direct costs of $124 billion and a further cost of $138 billion due to lost job productivity.

Cancer is the second leading cause of death in the United States, costing the health care system approximately $174 billion. Diabetes, obesity, and Alzheimer disease are endemic, and their prevalence rates will continue to rise with an aging population. Being able to address the anticipated rise in health care costs due to the aging population is simply not sustainable.

A new approach to care delivery is required. We are saddled with expensive, inefficient health care information technology (HIT) that has severed the personal connection between doctors and patients as well as between nurses and patients. If we do not change how care is delivered in this country, the health care system will collapse into a sea of red ink.

The move to value-based care is sometimes cited as a way to prepare for an aging population. But value-based models depend on enough patient volume to make the model work. Doctors and nurses are stressed enough due to inefficient HIT such as electronic health records, which were designed as billing systems that do not accommodate health care workflows. HIT needs to make the transition from data collection to supporting higher levels of productivity.

Appropriate strategies to decrease the incidence of chronic diseases and the associated costs to the health care system are critical if all Americans are to have appropriate access to care. For instance, a decrease of chronic diseases by 10% would result in savings of greater than $100 billion. Using primary and secondary prevention strategies that rely upon lifestyle changes are extremely cost-effective and will improve the quality of life for the aging population. In particular, improved education to the at-risk population will further enhance the positive effect on cost upon the health care system.

The 21st Century Cures Act mandates that patients have unfettered access to their medical records. Yet navigating through the maze of laboratory and imaging reports and physician notes with current technology is a daunting task for patients. We need to provide an organized approach to this information, with patient-approved secure access to medical records available to all providers caring for the patient. Utilizing Artificial Intelligence (AI) to improve patient medical literacy would also be critical for cost-effective management.

Better technology will also support remote patient monitoring. This will enable the development of virtual care paradigms that will further enhance the ability of health care providers to extend and improve care to the at-risk population, concentrating efforts to the high-cost patient using population health powered by better data and analysis.

The Healthy Lifestyle Program I oversaw at Roper St. Francis Healthcare is an example of the kind of program needed to prepare for the aging population tsunami. The cardiometabolic program is aimed at reducing the risk of chronic disease, normalizing metabolic abnormalities, decreasing the need for medications, and improving the overall fitness and functionality of the patient.

Fine-tuning the patient’s diet and setting fitness goals are essential to this approach. Thus, patients meet with a dietitian regularly and adjust their diet to a more balanced and healthier plan. Regularly scheduled small group exercise sessions with “homework” assignments for non-gym days improve fitness. This reduces overall metabolic abnormalities and improves functionality, particularly in patients previously limited by orthopedic issues. Programs such as these need to multiply many times over and eventually become standard for care.

It is past time for technology to create efficiencies and boost performance in health care as it has done in other industries. Despite its failings to date, improved HIT is the only way the current system can handle our nation’s aging population. Technology designed by clinicians for clinicians can restore the doctor-patient connection, empower remote care, and make population health more efficient. Only then will the current health care system be able to accommodate our aging population.

Dr Ciccone is the Chief Medical Officer of Document Storage Systems, Inc. A practicing cardiologist since 1982 and a leading advocate for better health IT, Dr Ciccone is board certified in internal medicine and cardiovascular disease and has additional board certification in integrative and holistic medicine.

Pareidolia

- from the painting “Fish Houses, Monhegan Island” by Sylvia Alberts

Richard Berlin, MD

I remember watching Sylvia paint three rough pine buildings raised on stilts, each with a wide ramp to roll catch through a yawning door, their floors soaked pink and green with fluids spilled from prey, a Skull and Crossbones flapping the pole.

But tonight it’s twenty years and two hundred leagues from the sea, her painting suddenly a family portrait—weather-beaten me in the middle with worried-window-eyes, door contorted as Munch’s scream, my wife sharing our dark inner wall, with her outside clapboards lit yellow by summer sun, our teenage daughter a detached building without an entrance, eyes measuring a changing tide.

And with one slow blink my reality shifts back to pandemic winter, the painting at rest on the mantle, choices made long ago drifted full circle, daughter, husband, and grandchildren beached back home, our sheltered—in-place family sprawled around the fireplace, lost in a recording of Treasure Island, Captain Flint perched on Long John Silver’s shoulder and squawking X marks the spot!, my gaze refocused on gold doubloons with familiar faces spilled at my feet.

Pareidolia: the tendency to perceive a specific, often meaningful image in a random or ambiguous visual pattern.
Important Safety Information

Boxed Warning: 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.

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 above.

- **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**, 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. It may also occur after discontinuation of treatment. Given these considerations, CAPLYTA should be prescribed in a manner most likely to reduce the risk of tardive dyskinesia. 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.

- **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.
See Its Efficacy at CAPLYTAHCP.COM

Choose CAPLYTA to help control your patients’ symptoms—with a metabolic, weight, and EPS profile similar to placebo in 4- to 6-week trials1

- Antipsychotic drugs have been reported to cause1:
  - Hyperglycemia, diabetes, dyslipidemia, and weight gain. Blood glucose, weight, and lipids should be monitored periodically during long-term treatment.
  - Tardive dyskinesia (TD), which may increase as the duration of treatment and cumulative dose increases, and can develop after brief treatment periods or after discontinuation. See full Important Safety Information, including Boxed Warning, below.

- 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, moderate or strong CYP3A4 inhibitors and UGT 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 somnolence/sedation (24% vs. 10%) and dry mouth (6% vs. 2%).

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

**CONTRAINDICATIONS**

**CAPLYTA** is indicated for the treatment of schizophrenia in adults.

**INDICATIONS AND USAGE**

patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analysis of placebo-controlled trials (mood disorders, schizophrenia, or other psychoses) showed a statistically significant (p < 0.001) increase in mortality in patients treated with antipsychotic drugs compared to placebo. This mortality difference was observed at an exposure of 1.8 to 11.8 months (median duration 5.8 months).

In pooled data from short-term (4- to 6-week), placebo-controlled trials of adult patients with dementia-related psychosis, the all-cause mortality in patients treated with **CAPLYTA** compared to patients treated with placebo was 2.4% and 0.8%, respectively. The rates of death from all causes for **CAPLYTA** and placebo were 3.9% and 1.1%, respectively. Deaths caused by cardiac and cerebrovascular diseases were significantly higher in patients treated with **CAPLYTA** compared to patients treated with placebo. The mortality difference was statistically significant (p < 0.001). Of these deaths, 84% of deaths in patients treated with **CAPLYTA** and 72% of deaths in patients treated with placebo were considered related to the underlying dementia disease process. Of the deaths that were considered related to the underlying dementia disease process, CAPLYTA and placebo were 0.7% and 0.2%, respectively. The rates of syncope for **CAPLYTA** and placebo were 0.7% and 0.4%, respectively. There were no meaningful differences in the rates of syncope across treatment groups. The rates of syncope were low, ranging from 0.2% to 1.1%.

**ORAL CYANIDE REACTIONS**

**CAPLYTA** should be prescribed in a manner most likely to reduce the risk of oral cyanide reactions. In patients with a pre-existing low WBC or ANC or a history of drug-induced leukopenia or neutropenia, perform a complete blood count (CBC) prior to initiating treatment with **CAPLYTA**.

**Dosing Adjustments**

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

**NEUROLOGIC MALIGNANT SYNDROME**

Neuroleptic Malignant Syndrome (NMS), a potentially fatal syndrome, has been reported in association with the use of antipsychotic drugs. The syndrome is characterized by hyperpyrexia, muscle rigidity, delirium, and autonomic instability. Additional signs may include elevated creatine phosphokinase, myoglobin (hemoglobinuria), and acute renal failure. In patients with NMS, treatment should be immediate and supportive care, including close medical supervision and monitoring.

**Tardive Dyskinesia**

Tardive dyskinesia is a syndrome of potentially irreversible, involuntary, dyskinetic movements. Patients may develop these movements after being treated with antipsychotic drugs for relatively short periods of time. The risk of developing tardive dyskinesia is increased in older patients, especially women, but it is not possible to predict which patients will be affected. The long-term risk of developing tardive dyskinesia is unknown. In controlled clinical trials, tardive dyskinesia developed in 0.9% of patients treated with **CAPLYTA** in 102 minutes of exposure and 108 had at least 1 year of exposure to **CAPLYTA**. The rates of death from all causes for **CAPLYTA** and placebo were 3.9% and 1.1%, respectively. Deaths caused by cardiac and cerebrovascular diseases were significantly higher in patients treated with **CAPLYTA** compared to patients treated with placebo. The mortality difference was statistically significant (p < 0.001). Of these deaths, 84% of deaths in patients treated with **CAPLYTA** and 72% of deaths in patients treated with placebo were considered related to the underlying dementia disease process. Of the deaths that were considered related to the underlying dementia disease process, CAPLYTA and placebo were 0.7% and 0.2%, respectively. The rates of syncope for **CAPLYTA** and placebo were 0.7% and 0.4%, respectively. There were no meaningful differences in the rates of syncope across treatment groups. The rates of syncope were low, ranging from 0.2% to 1.1%.

**ADVERSE REACTIONS**

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

**Somnolence/Sedation**

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

**Cerebrovascular Adverse Reactions, Including Stroke**

**Elderly** patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analysis of placebo-controlled trials (mood disorders, schizophrenia, or other psychoses) showed a statistically significant (p < 0.001) increase in mortality in patients treated with antipsychotic drugs compared to placebo. This mortality difference was observed at an exposure of 1.8 to 11.8 months (median duration 5.8 months).

In pooled data from short-term (4- to 6-week), placebo-controlled trials of adult patients with dementia-related psychosis, the all-cause mortality in patients treated with **CAPLYTA** compared to patients treated with placebo was 2.4% and 0.8%, respectively. The rates of death from all causes for **CAPLYTA** and placebo were 3.9% and 1.1%, respectively. Deaths caused by cardiac and cerebrovascular diseases were significantly higher in patients treated with **CAPLYTA** compared to patients treated with placebo. The mortality difference was statistically significant (p < 0.001). Of these deaths, 84% of deaths in patients treated with **CAPLYTA** and 72% of deaths in patients treated with placebo were considered related to the underlying dementia disease process. Of the deaths that were considered related to the underlying dementia disease process, CAPLYTA and placebo were 0.7% and 0.2%, respectively. The rates of syncope for **CAPLYTA** and placebo were 0.7% and 0.4%, respectively. There were no meaningful differences in the rates of syncope across treatment groups. The rates of syncope were low, ranging from 0.2% to 1.1%.

**Somnolence/Sedation**

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

**SERIOUS CARDIOVASCULAR EVENTS**

Serious cardiovascular (e.g., heart failure, sudden death) or infectious events (e.g., pneumonia) in nature **CAPLYTA** is not approved for the treatment of patients with dementia-related psychosis.

**Congestive Heart Failure**

**CAPLYTA** is contraindicated in patients with history of congestive heart failure (CHF) or significant CHF manageable. The risk of serious cardiovascular (e.g., heart failure, sudden death) or infectious events (e.g., pneumonia) in nature **CAPLYTA** is not approved for the treatment of patients with dementia-related psychosis.

**CHF**

**CAPLYTA** is contraindicated in patients with history of congestive heart failure (CHF) or significant CHF manageable. The risk of serious cardiovascular (e.g., heart failure, sudden death) or infectious events (e.g., pneumonia) in nature **CAPLYTA** is not approved for the treatment of patients with dementia-related psychosis.

**PAPULAR RASH**

**CAPLYTA** is contraindicated in patients with papular rash, and generalized rash, and urticaria.

**ANGIOEDEMA**

**CAPLYTA** is contraindicated in patients with angioedema.

**PREGNANCY**

Like other antipsychotic drugs, **CAPLYTA** may cause somnolence, postural hypotension, and motor and sensory instability, which may lead to falls and, consequently, fractures and other injuries. For patients with diseases, conditions, or other risk factors that increase the likelihood of falling, **CAPLYTA** should be used with caution in patients who may experience more profound and prolonged postural hypotension, at least until they are reasonably certain that therapy with **CAPLYTA** does not affect the ability to reduce core body temperature. Strenuous exercise, exposure to extreme environments (e.g., hot environments, fever), and infections (e.g., influenza) have been associated with exacerbated hyperpyrexia, which can occur at low doses.</p>
Helping Pediatric Patients and Families Through the Holidays

Lisa Hunter Romanelli, PhD

Although the December holidays this year may be more normal than those of 2020, the psychological stressors of the pandemic are still in play. For many families, the pressure to get back to normal may itself be a stressor. For example, many parents are wrestling with whether to share a meal with unvaccinated family members or to expose vulnerable older adults, friends, and family to unvaccinated young children.

Furthermore, holidays can be difficult for children and teenagers with depression, anxiety, and other disorders, even during the best of times. Thanks to the many issues related to the pandemic, these have not been the best of times. The American Academy of Pediatrics, American Academy of Child and Adolescent Psychiatry, and Children’s Hospital Association recently declared a national emergency in child and adolescent mental health due to the skyrocketing incidence of mental illness, particularly among teenagers, during the pandemic.

Also more pronounced during this holiday season are experiences of loss and grief. According to findings from a recent study, approximately 140,000 children have lost a parent or grandparent caregiver due to the COVID-19 virus, with losses concentrated among children of color.1

All these factors may make this year’s holiday season difficult for young patients and their families. That makes this a good time to redouble efforts on behalf of pediatric patients.

A basic step is simply to use the holidays as a reason to check in with patients and caregivers as follows: “So the holiday season is coming up. How are you feeling about that?” More probing questions can follow, depending on the response.

Because family support is a strong predictor of child resilience,2 checking in with caregivers is important. Psychiatrists can listen to caregivers’ concerns about the upcoming holidays and their child’s emotional state. Sometimes being heard may be sufficient. If not, clinicians can continue to educate parents about how to deal with their child’s mental health challenges, using the holidays as a jumping-off point.

It is important to emphasize the importance of structure when talking with older children and teenagers as well as parents and/or guardians of younger children. One reason for December meltdowns or increases in depressive symptoms may simply be due to the lack of sleep as well as changes in routine when schools are not in session. Remind patients and families that keeping to normal bedtimes and meal-times—standard advice for reducing stress during any holiday season—is more important this year than ever.

Patients and families who are mourning may need special support. In addition to monitoring patients for signs that healthy grief is sliding into depression, consider suggesting self-help steps such as joining a support group. The National Alliance for Children’s Grief offers a list of local bereavement resources by state and region, as well as its own resources. The Dougy Center also has resources for dealing with bereavement, including a grief support program finder.

Further, some patients may suffer from seasonal affective disorder (SAD). Although SAD commonly begins in young adulthood, it can affect adolescents. A diagnosis of SAD requires at least 2 instances of depression that begin in fall or winter and remit in spring. Light therapy is the gold standard treatment for SAD, often combined with cognitive behavioral therapy and medication.

Finally, clinicians should, as always, carefully monitor their own emotional health. The stressors that affect patients’ families during the holidays may also affect psychiatric professionals and their families. Self-care routines, including opportunities to share emotional burdens with close friends or trusted colleagues, take on greater importance in proportion to the distress manifested by one’s patients.

Dr Romanelli is CEO of The REACH Institute, a nonprofit organization that trains primary care providers, therapists, and health care institutions in evidence-based therapies for child and adult mental health issues. She is also a licensed psychologist with expertise in cognitive behavioral therapy in clinical practice in Princeton, New Jersey.

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Physician Advisor to Freespira
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When Suicide Is Not a Suicide: An Epilogue

H. STEVEN MOFFIC, MD
Award-winning psychiatrist

Watch these Mental Health Minute videos on psychiatrictimes.com
Many Bipolar Update columns concerning lithium have focused on lithium’s advantages. The well-known downsides, including renal impairment, have also been discussed. However, a recent consultation reminded me that there is an infrequent, but important, toxic effect of lithium that deserves increased awareness: the Syndrome of Irreversible Lithium-Effectuated Neurotoxicity, or SILENT. First named in the 1980s, SILENT was diagnosed in 90 case reports in peer-reviewed publications as of 2005, starting in 1949 when lithium chloride was being used as a substitute for table salt.

The clinical profile of SILENT varies, but persistent cerebellar dysfunction is the most common finding, with extrapyramidal symptoms also typically present. Many of these cases involve insidious progression in patients on normal or low therapeutic levels of lithium. The first sign may be decreased alertness or slight apathy, followed by muscular rigidity or fasciculations and mild ataxia. These symptoms increase and become severe, and then impaired consciousness with a stupor-like presentation can develop.

When lithium is stopped, some or all of these symptoms may persist beyond 2 months, with some reports describing continued symptoms for 5 years. Most cases have residual impairments such as ataxia and dysarthria that continue for 1 year. Sometimes there is persisting cognitive dysfunction with memory loss and other symptoms of dementia. In other cases, additional atypical symptoms accompany the core features, including nystagmus, papilledema, and choreoathetoid movements suggestive of tardive dyskinesia.

SILENT’s cause is unknown. Demyelination has been found on biopsy of peripheral nerves and may occur in the cerebellum and elsewhere. This may account for the persistence of the neurological sequelae.

Precipitating or predictive factors may include diagnosis of schizoaffective disorder, marked psychosis, abnormal EEG prior to treatment, preexisting neurological illnesses including Alzheimer disease, and fever—especially high fever. Readers may recall the famous 1970s cases of neurotoxicity arising from the use of lithium plus haloperidol. All patients in those cases had very high fevers and high lithium levels, and they are now thought to have had cases of SILENT. Some other possible contributing factors could be hypertension, heart failure, rapid lowering from high lithium levels, and epilepsy.

To prevent SILENT, it may be helpful to avoid high lithium levels through regular and frequent monitoring (eg, every 4–6 months). If symptoms develop, rapidly taper and discontinue lithium. Treat persisting symptoms with appropriate physical rehabilitation and cognitive training as you would for dementia.

The other side of the coin on lithium neurotoxicity, as discussed in a previous column, is the positive neuroprotective effects of lithium that benefit many patients. In a recent pilot study, for example, 12 patients recovering from stroke were prescribed open-label lithium for 60 days (target levels, 0.4–0.6 mEq/L). Gray matter volume as measured by MRI increased numerically (but not significantly; \( P = .07 \)), and there was a significant correlation between higher lithium dose and gray matter volume increase (\( P = .004 \)) and improved verbal memory (\( P = .05 \)).

In conclusion, lithium’s benefits to brain health are substantial, but there are rare cases of serious toxicity that should be detected as early as possible.

Dr Osser is an associate professor of psychiatry at Harvard Medical School and codirector of the US Department of Veterans Affairs’ National Bipolar Disorder Telehealth Program, in Brockton, Massachusetts. The author reports no conflicts of interest concerning the subject matter of this article.

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Promising Results for a New Treatment Option for Patients With Narcolepsy

According to Kushida, who is lead author of the study and professor of psychiatry and behavioral sciences at Stanford University School of Medicine, narcolepsy affects 1 in 2000 individuals, and is equally prevalent in men and women. Common symptoms include cataplexy, hallucinations, EDS, sleep paralysis, and sleep disruption. There are 2 types of narcolepsy: NT1, in which patients experience cataplexy and have low levels of hypocretin 1/orexin A, and NT2, in which patients do not experience cataplexy absent and levels of hypocretin 1/orexin A are not low.

In the study, 107 patients with narcolepsy were randomized to receive the study medication while 105 received placebo. Change from baseline in mean sleep latency on the Maintenance of Wakefulness Test, Clinical Global Impression-Improvement (CGI) ratings, and weekly cataplexy attacks were the 3 main end points; changes from baseline on the Epworth Sleepiness Scale were the secondary end points. The trial had a 3-week screening period followed by a 13-week treatment regimen and a 1-week follow-up period. The patients received 4.5 g during the first week of treatment, 6 g during weeks 2 to 3, 7.5 g during weeks 4 through 8, and 9 g during weeks 9 to 13.

The study was conducted internationally. Baseline demographics were well balanced across both arms of the study. The mean age was 31 and 32 years for the medication and placebo arms, respectively. Most patients were female, and about 75% had NT1. Most patients (80.7%) were taking at least 1 concomitant medication, usually a stimulant.

Kushida et al found the study medication was efficacious across all 3 main end points. For instance, he explained, “The increase in sleep latency was significantly greater with the once-nightly sodium oxybate versus placebo and at week 3 for the 6-g dose.” Similarly, there was a significant improvement on the CGI scale and a significant decrease in weekly cataplexy attacks for participants in the active arm versus those receiving placebo.

And, although patients experienced adverse effects, they were generally considered mild. The most common adverse effects included nausea, headache, vomiting, dizziness, enuresis, decreased appetite, anxiety, hyperhidrosis, and decreased weight.

Krahn, professor of psychiatry in The Mayo Clinic College of Medicine with joint appointment in the Department of Psychiatry and Psychology and the Division of Pulmonary Medicine, also discussed the paper and shared her enthusiasm for the results. “The data from this paper is incredibly valuable to those of us who treat patients with narcolepsy since it shows that patients are better able to stay awake as measured by the Maintenance of Wakefulness Test and by the excess sleepiness score. It also shows that cataplexy is controlled on once-a-night sodium oxybate as compared with placebo. And lastly, that patient’s quality of life can improve. So, on all 3 of those important measures, this medication appears to be effective, and very useful to the medical community and our patients.”

Kushida concurred. “These types of modified release formulations are commonly applied to different therapies, mainly to decrease patient burden,” he said. “And since they can improve adherence with this regimen, [they can] enhance the overall patient experience. For chronic medical conditions, such as narcolepsy, this is very important. Because, as we all know, narcolepsy is significantly debilitating, [affecting] almost every aspect of the patient’s life when it’s not successfully treated.”

Moreover, Kushida noted that once-nightly sodium oxybate has also received orphan drug designation by the US Food and Drug Administration based on the possibility that it may be clinically superior to the twice-a-night formulation that is currently approved for this indication.

Both Kushida and Krahn find this exciting news, as there are advantages of the once-nightly treatment regimen. For instance, Kushida noted the simpler regimen may result in better adherence. It also may benefit the patient’s bed partner, whose sleep could have been disrupted for the twice-nightly regimen. Plus, the plasma concentrations decline steadily after the first and only CMAX, which occurs early post-dose based on the psychopharmacology of the once-nightly dosing. Therefore, Kushida believes it will be associated with fewer falls.

Krahn added that many patients become dissatisfied in pursuing the treatment when it requires twice-nightly dosing, and this newer, simplified regimen may mean more patients are willing to try this treatment option.

The speakers also discussed the intriguing data on sleep architecture and the need for further studies. “We all want medications, where they make a difference for the patient’s symptoms, but that the levels of the medication in the patient’s body aren’t higher than they need to be, and are just released in a more continuous gradual way and come closer to normalizing sleep,” Krahn said. “That’s what we want for our patients with all of our therapies, and with the once nightly form of therapy, the CMAX data is very promising.”

“This study was actually the first randomized control trial demonstrating the efficacy and safety of a 7.5 g of sodium oxybate,” Kushida added. “And given that the efficacy was nearly comparable to the 9-g dose, compared to placebo, this may afford confidence for prescribers and patients that a lower dose can be effectively used in practice.”

He also noted this was the first published study describing a statistical reduction of cataplexy compared to placebo with a 4.5-g dose, and that this study met the clinical guidelines from the American Academy of Sleep Medicine across all 3 doses.

“As psychiatrists, we have many medications used for other conditions where we have to prepare our patients to wait a long time to have the treatment response. So, the data that suggests and indicates that cataplexy can improve after 1 week I think will be very well received by our patients,” Krahn added. “Many have to be embarrassed or maybe even put at risk if their cataplexy continues. And if this medication can help them, I think that that is a very important finding.

REFERENCE
"You know, I am not typically attracted to Black men, but..." said my non-Black attending as we walked down the hallway to our next patient. I did not listen to the rest. Fortunately, she was not looking at me as she spoke. If she had been, my facial expression would have clearly communicated my disdain. Listening to this attending sexualize Black men, which is a longstanding racist behavior, was not something I ever wanted to do—let alone as I was being supervised during a clinical rotation in my first year of residency. Racist statements are cognitively disarming when I am trying to learn how to be a psychiatrist. But, as a Black resident, I have learned to deal with them—I have to.

I thought back to medical school when I was summoned by a senior attending to discuss a psychiatric patient. I ruffled through my notes, reviewing my patient formulation and speculating about the questions he might ask me. I took a deep breath and pushed open the door, making a mental note of my proposed medication management. "Ah, Amanda," said the senior attending, looking up from his desk. "I wanted to ask you. This patient to whom you are assigned..."

I frowned. "I don’t think there is anything easy about being Black, female, and having a mental illness," I said. "Unfortunately, I can’t give tips about scholarships because I didn’t have one as a college student at Yale." His jaw dropped.

Conversations like these are some of the least troublesome I have encountered. In fact, I have come to expect them, and, since I grew up in predominantly white spaces, I found insensitive statements with racist assumptions that I somehow less-than-to-be commonplace. As a child, they upset me, but I had coaching from brilliant parents who are professionals at navigating racism.

Some interactions with supervisors are more troubling. Attendings have deleted my notes documenting racist events in the hospital, stated some-what ominously that my activism can “hurt or help me” in my written evaluations, or told me that I have.“Yeah, and then the visiting nurse came in...and you know, she was Black...” My ears perked up immediately. The supervisor let the patient finish and then replied, “I noticed you mentioned the race of the visiting nurse. Why? Did you have an issue with the fact that she was Black? Was racism at play there?” The actions of that supervisor spoke volumes for me.

Actions are important, too. Once, a supervisor and I were listening to a white patient discuss his experience. Quite randomly, he stated, “I noticed you mentioned the race of the visiting nurse.” The supervisor may be safe to discuss racism with abstractly, but not in real-time clinical circumstances.

In such an example, the supervisor may feel that racism plays a role in the medical system at large, but if I point out that a white staff member in their unit seems to be treating patients differentially based on race, the supervisor becomes angry or defensive, rather than investigative and concerned. Sometimes the supervisor sets the temperature before I test it. If they make an offensive statement like, “You know where the most child abuse happens? In Native American reservations...” then I know that the supervisor is unsafe. On the contrary, if they make a statement acknowledging the impact of racism, stating the actual word racism, or even better, white supremacy, then they are on the safer end of the spectrum.

Concluding Thoughts
To be sure, there are many positive aspects of the supervisor-supervisee relationship. As a resident, supervision is crucial to my learning and development as a psychiatrist. The invaluable opportunity to present and discuss patients with a senior attending is a central part of psychiatric training. It is uncomfortably common to have unsafe supervisors, so additional planning as a minority supervisee is required, which often results in missed opportunities for important conversations about racism to occur. However, encountering truly safe supervisors is invigorating, because so few spaces are safe to discuss racism. In fact, I firmly believe that safe supervisors are the best supervisors. They feel that supervisees, like me, have knowledge to contribute through our lived experiences and our scholarship. They listen to us in addition to teaching us, and, in situations where racism plays out in real time, they help us.

Dr Calhoun is an adult/child psychiatry resident at Yale Child Study Center/Yale School of Medicine. She is also a Public Voices Fellow of the OpEd Project at Yale University.

REFERENCES
Give me treatment that starts strong and stays strong

• ARISTADA is proven effective in adult patients with schizophrenia¹
• Start strong with single-day initiation (ARISTADA INITIO regimen)¹,²*
• Stay strong with the ARISTADA 2-month dose (1064 mg)³†

*The ARISTADA INITIO regimen is defined as a single injection of ARISTADA INITIO (675 mg) given in conjunction with a single 30 mg dose of oral aripiprazole.²
†Additional dosing options are available: 441 mg monthly, 662 mg monthly, and 882 mg monthly or every 6 weeks.¹

Important dosing considerations for ARISTADA INITIO and ARISTADA

• For patients who have never taken aripiprazole, establish tolerability with oral aripiprazole prior to initiating ARISTADA® (aripiprazole lauroxil) or ARISTADA INITIO® (aripiprazole lauroxil)²°
• ARISTADA INITIO and ARISTADA are only to be administered as an intramuscular injection by a healthcare professional¹²
• There are 2 ways to start treatment with ARISTADA. If not starting ARISTADA with the ARISTADA INITIO regimen, administer 21 consecutive days of oral aripiprazole with the first ARISTADA injection¹
• Adjust ARISTADA dose as needed. When making dose and dosing interval adjustments, consider the pharmacokinetics and prolonged-release characteristics of ARISTADA. ARISTADA INITIO is a single dose, and adjustments are not possible¹³
• If/when a dose of ARISTADA is missed, administer the next injection as soon as possible. Concomitant supplementation following a missed dose may be recommended depending on the time elapsed since last injection. See full Prescribing Information for more information¹

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

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

IMPORTANT SAFETY INFORMATION FOR ARISTADA INITIO AND ARISTADA

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

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

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

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

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

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

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

**Metabolic Changes:** Atypical antipsychotic drugs have been associated with metabolic changes that include:

- **Hyperglycemia/Diabetes Mellitus:** Hyperglycemia, in some cases extreme and associated with ketoacidosis, coma, or death, has been reported in patients treated with atypical antipsychotics. There have been reports of hyperglycemia in patients treated with oral aripiprazole. Patients with diabetes should be regularly monitored for worsening of glucose control; those with risk factors for diabetes should undergo baseline and periodic fasting blood glucose testing. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia, including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia should also undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients require continuation of antidiabetic treatment despite discontinuation of the suspect drug.

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

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

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

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

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

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

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

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

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

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

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

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

**Commonly Observed Adverse Reactions:** In pharmacokinetic studies the safety profile of ARISTADA INITIO was generally consistent with that observed for ARISTADA. The most common adverse reaction (≥5% incidence and at least twice the rate of placebo reported by patients treated with ARISTADA 441 mg and 882 mg monthly) was akathisia.

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

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

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

**References:**
ARISTADA INITIO® (aripiprazole lauroxil) extended-release injectable suspension, for intramuscular use

BRIEF SUMMARY OF PRESCRIBING INFORMATION

(For complete details, please see full Prescribing Information and Medication Guide.)

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

- Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modular duration of 10 weeks), largely in patients taking typical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.5% in the placebo group.

Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature.

Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. ARISTADA INITIO is not approved for the treatment of patients with dementia-related psychosis.

INDICATIONS AND USAGE: ARISTADA INITIO, in combination with oral aripiprazole, is indicated for the treatment of schizophrenia in adults.

CAUTIONS REGARDING ADVERSE REACTIONS: In placebo-controlled trials with aripiprazole, the incidence of adverse reactions was similar to placebo, except for the following:

- Dry mouth
- Constipation
- Fatigue

ADDITIONAL INFORMATION

- Tardive Dyskinesia: Symptoms can occur at low doses, they occur more frequently and with greater severity in elderly patients, especially women.

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

ARISTADA INITIO has been evaluated for safety in 170 adult patients in pharmacokinetic studies and 1403 adult patients in controlled clinical trials. Safety and tolerability were similar to placebo. The most common adverse reactions reported were injection site reactions, injection site pain, and injection site reaction (anaphylactic reaction, angioedema, laryngospasm, pruritus/urticaria, or other hypersensitivity reactions). In placebo-controlled trials with aripiprazole, the incidence of injection site reactions was similar to placebo, except for the following:

- Injection site pain
- Injection site reaction

Use in Specific Populations

- Pregnancy: There is a pregnancy exposure registry that monitors the use of oral aripiprazole. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. In the clinical trials program, post-approval use of oral aripiprazole. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. In the clinical trials program, patients treated with aripiprazole, the incidence of injection site reactions was similar to placebo, except for injection site pain, injection site reaction (anaphylactic reaction, angioedema, laryngospasm, pruritus/urticaria, or other hypersensitivity reactions).

- Nursing Mothers: Per routine post-marketing reporting, no specific information on the excretion of aripiprazole in human milk is available. Because many drugs are excreted in human milk, consider human milk feeding patterns and the importance of the drug to the mother when deciding to use aripiprazole in a nursing mother. If you choose to use aripiprazole in a nursing mother, monitor the infant for adverse reactions.

- Pediatric Use: There are no adequate and well-controlled studies in pregnant women. Therefore, aripiprazole should not be used in pregnant women. The safety and effectiveness of aripiprazole for the treatment of schizophrenia in patients 18 years of age and older have been established in controlled clinical trials. There is no information on the use of aripiprazole in children and adolescent patients due to the potential of increased adverse reactions to antipsychotics, consideration for the age-appropriate use of antipsychotics, and clinical need for antipsychotic therapy. Therefore, aripiprazole should not be used in children and adolescent patients. The safety and effectiveness of aripiprazole for the treatment of bipolar I disorder in patients 18 years of age and older have been established in controlled clinical trials. There is no information on the use of aripiprazole in children and adolescent patients due to the potential of increased adverse reactions to antipsychotics, consideration for the age-appropriate use of antipsychotics, and clinical need for antipsychotic therapy. Therefore, aripiprazole should not be used in children and adolescent patients. The safety and effectiveness of aripiprazole for the treatment of schizophrenia in patients 18 years of age and older have been established in controlled clinical trials. There is no information on the use of aripiprazole in children and adolescent patients due to the potential of increased adverse reactions to antipsychotics, consideration for the age-appropriate use of antipsychotics, and clinical need for antipsychotic therapy. Therefore, aripiprazole should not be used in children and adolescent patients. The safety and effectiveness of aripiprazole for the treatment of bipolar I disorder in patients 18 years of age and older have been established in controlled clinical trials. There is no information on the use of aripiprazole in children and adolescent patients due to the potential of increased adverse reactions to antipsychotics, consideration for the age-appropriate use of antipsychotics, and clinical need for antipsychotic therapy. Therefore, aripiprazole should not be used in children and adolescent patients.
Seizures: As with other antipsychotic drugs, use ARISTADA INITIO cautiously in patients with a history of seizures or with conditions that lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

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

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

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

ADVERSE REACTIONS

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

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

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

ARISTADA (Aripiprazole Lauroxil) Trials in Adults with Schizophrenia

Commonly Observed Adverse Reactions with Aripiprazole Lauroxil: The most common adverse reaction (incidence 2%-5% and at least twice the rate of placebo in patients treated with aripiprazole lauroxil) was akathisia.

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

Injection Site Reactions

ARISTADA INITIO

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

ARISTADA (Aripiprazole Lauroxil)

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

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

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

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

Cardiac – angina pectoris, tachycardia, palpitations

Gastrointestinal disorders – constipation, dry mouth

General disorders – asthenia

Musculoskeletal – muscular weakness

Nervous system disorders – dizziness

Psychiatric disorders – anxiety, suicide

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

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

Eye Disorders: photophobia, diplopia

Gastrointestinal Disorders: gastroesophageal reflux disease

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

Hepatobiliary Disorders: hepatitis, jaundice

Immune System Disorders: hypersensitivity

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

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

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

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

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

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

Renal and Urinary Disorders: urinary retention, nocturia

Reproductive System and Breast Disorders: erectile dysfunction, gynecomastia, menstrual irregular, amenorrhea, breast pain, priapism

Respiratory, Thoracic, and Mediastinal Disorders: nasal congestion, dyspnea

Skin and Subcutaneous Tissue Disorders: rash, hyperhidrosis, pruritus, photosensitivity reaction, alopecia, arcburia

Vascular Disorders: hypertension, hypotension

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

DRUG INTERACTIONS

Table 1: Clinically Important Drug Interactions With ARISTADA INITIO

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Clinical Impact</th>
<th>Intervention</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong CYP3A4 Inhibitors and CYP2D6 Inhibitors</td>
<td>Concomitant use of oral aripiprazole with strong CYP3A4 or CYP2D6 inhibitors increased the exposure of aripiprazole compared to the use of oral aripiprazole alone</td>
<td>Avoid concomitant use of ARISTADA INITIO with strong CYP3A4 or strong CYP2D6 inhibitors because the dosage of ARISTADA INITIO cannot be modified</td>
<td>Itraconazole, clarithromycin, quinidine, fluoxetine, paroxetine</td>
</tr>
<tr>
<td>Strong CYP3A4 Inducers</td>
<td>Concomitant use of oral aripiprazole and carbamazepine decreased the exposure of aripiprazole compared to the use of oral aripiprazole alone</td>
<td>Avoid concomitant use of ARISTADA INITIO with strong CYP3A4 inducers because the dosage of ARISTADA INITIO cannot be modified.</td>
<td>Carbamazepine, rifampin</td>
</tr>
</tbody>
</table>

Antihypertensive Drugs

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

Intervention: Avoid concomitant use of ARISTADA INITIO with antihypertensive drugs because the dosage of ARISTADA INITIO cannot be modified.

Examples: carvedilol, lisinopril, prazosin

Benzodiazepines

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

Intervention: Avoid concomitant use of ARISTADA INITIO with benzodiazepines because the dosage of ARISTADA INITIO cannot be modified.

Examples: lorazepam

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry: There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ARISTADA INITIO during pregnancy. For more information, contact the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or visit http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/.
Risk Summary: Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. Limited published data on aripiprazole use in pregnant women are not sufficient to inform any drug-associated risks for birth defects or miscarriage. No teratogenicity was observed in animal reproductive studies with intramuscular administration of aripiprazole lauroxil to rats and rabbits during organogenesis at doses up to 8 and 23 times, respectively, the maximum recommended human dose (MRHD) of 675 mg based on body surface area (mg/m²). However, aripiprazole caused developmental toxicity and possible teratogenic effects in rats and rabbits. The background risk of major birth defects and miscarriage for the indicated population are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. Advise pregnant women of the potential risk to a fetus.

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

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

Animal Data for Aripiprazole: Pregnant rats were treated with oral doses of 3, 10, and 30 mg/kg/day which are approximately 1 to 10 times the oral MRHD of 30 mg/day based on mg/m² of aripiprazole during the period of organogenesis. Treatment at the highest dose caused a slight prolongation of gestation and delay in fetal development, as evidenced by decreased fetal weight, and undescended testes. Delayed skeletal ossification was observed at 3 and 10 times the oral MRHD based on mg/m².

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

In pregnant rabbits treated with oral doses of 10, 30, and 100 mg/kg/day which are 2 to 11 times human exposure at the oral MRHD based on AUC and 6 to 65 times the oral MRHD based on mg/m² of aripiprazole during the period of organogenesis decreased maternal food consumption and increased abortions were seen at the highest dose as well as increased fetal mortality. Decreased fetal weight and increased incidence of fused sternebrae were observed at 3 and 11 times the oral MRHD based on AUC.

In rats treated with oral doses of 3, 10, and 30 mg/kg/day which are 1 to 10 times the oral MRHD based on mg/m² of aripiprazole perinatally and postnatally (from day 17 of gestation through day 21 postpartum), slight maternal toxicity and slightly prolonged gestation were seen at the highest dose. An increase in stillbirths and decreases in pup weight (persisting into adulthood) and survival were also seen at this dose.

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

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

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

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

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

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

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

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

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

PATIENT COUNSELING INFORMATION

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

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

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

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

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

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

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

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

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

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

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

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

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

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

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases in which the clinical presentation includes both serious medical illnesses (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS. If a patient appears to require antipsychotic drug treatment after recovery from NMS, reintroduction of drug therapy should be closely monitored, since recurrences of NMS have been reported.

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

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible appear to increase as the duration of treatment and the cumulative dose of antipsychotic drugs administered to the patient increase, but the syndrome can develop even after relatively brief treatment periods at low doses, although this is uncommon.

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

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

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

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

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

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

In the long-term, open-label schizophrenia study with ARISTADA, 14% of patients with normal hemoglobin A1c (<5.7%) at baseline developed elevated levels (≥5.7%) post-baseline.

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

In the long-term, open-label schizophrenia study with ARISTADA, shifts in baseline fasting total cholesterol from normal (<200 mg/dL) to high (≥240 mg/dL) were reported in 1% of patients; shifts in baseline fasting LDL cholesterol from normal (<100 mg/dL) to high (≥160 mg/dL) were reported in 1% of patients; and shifts in baseline fasting triglycerides from normal (<150 mg/dL) to high (≥200 mg/dL) were reported in 6% of patients. In the same study, shifts in baseline fasting total cholesterol from borderline (200-299 mg/dL) to high (≥240 mg/dL) were reported in 15% of patients; shifts in baseline fasting LDL cholesterol from borderline (100 mg/dL and <160 mg/dL) to high (≥160 mg/dL) were reported in 6% of patients; and shifts in baseline fasting triglycerides from borderline (150 mg/dL and <200 mg/dL) to high (≥200 mg/dL) were reported in 35% of patients. In addition, the proportion of patients with shifts in fasting HDL cholesterol from normal (≥40 mg/dL) to low (<40 mg/dL) was reported in 15% of patients.

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

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

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

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

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

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

Orthostatic hypotension was reported for 2% of placebo patients treated in the ARISTADA 882 mg group (0.5%) and 2% of ARISTADA 441 mg and placebo groups in the 12-week schizophrenia efficacy study. In the long-term open-label schizophrenia study, orthostatic hypotension was reported for 1.0% of patients treated with ARISTADA. Orthostatic hypotension was defined as a decrease in systolic blood pressure ≥ 20 mmHg accompanied by an increase in heart rate ≥ 25 bpm when comparing standing to supine values.

Falls: Antipsychotics including ARISTADA may cause somnolence, postural hypotension, or 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 antipsychotic treatment and recurrently for those patients on long-term antipsychotic therapy.

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

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC)/absolute neutrophil count (ANC) and history of drug-induced leukopenia/neutropenia. In patients with a history of a clinically significant low WBC/ANC or drug-induced leukopenia/neutropenia, perform a complete blood count (CBC) frequently during the first few months of therapy. In such patients, consider discontinuation of ARISTADA at the first sign of a clinical decline in WBC or ANC. Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treat promptly if such symptoms or signs occur. Discontinue ARISTADA in patients with severe neutropenia (absolute neutrophil count < 1000/mm3) and follow their WBC until recovery.

Sources: As with other antipsychotic drugs, use ARISTADA cautiously in patients with a history of seizures or conditions that lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

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

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

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic agents. Consider using a lower starting dose, and monitor patients with clinically significant dysphagia/neuropenia for aspiration pneumonia.

ADVERSE REACTIONS

Clinical Studies Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates observed in practice.

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

Commonly Observed Adverse Reactions: The most common adverse reaction (incidence ≥ 5%) and at least twice the rate of placebo in patients treated with ARISTADA was akathisia. Table 2 shows Adverse Reactions Occurring at an Incidence of 2% or More in ARISTADA-Treated Patients. Adverse reactions associated with the use of ARISTADA (incidence of ≥ 2%) are depicted in Table 3 and Table 4. Adverse reactions that occurred in ≥ 2% of patients treated with ARISTADA in the 12-Week, Placebo-Controlled, Fixed-Dose Schizophrenia Trial are shown in Table 5.

Table 2: Adverse Reaction in 2% or More of ARISTADA-Treated Patients and That Occurred at a Greater Incidence Than Placebo-Treated Patients in the 12-Week, Placebo-Controlled, Fixed-Dose Schizophrenia Trial

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

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

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

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

Table 3: Incidence of EPS Compared to Placebo

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

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

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

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

Adverse Reactions Reported in Clinical Trials with Oral Aripiprazole: the following is a list of additional adverse reactions that have been reported in clinical trials with oral aripiprazole and not reported above for ARISTADA, Blood and Lymphatic System Disorders: thrombocytopenia
Cardiac Disorders: bradycardia, atrial flutter, cardiorespiratory arrest, atrioventricular block, atrial fibrillation, myocardial ischemia, myocardial infarction, cardiopulmonary failure
Eye Disorders: photophobia, diplopia
Gastrointestinal disorders: gastroesophageal reflux disease
General Disorders and Administration-Site Conditions: peripheral edema, chest pain, face edema
Hepatobiliary Disorders: hepatitis, jaundice
Immunologic System Disorders: hypersensitivity
Injury, Poisoning, and Procedural Complications: fall, heat stroke
Investigations: weight decreased, hepatic enzyme increased, blood glucose increased, blood lactate dehydrogenase increased, gamma glutamyl transpeptidase increased, blood prolactin increased, blood urea increased, blood creatinine increased, blood bilirubin increased, electrolydogram QT prolonged, glycosylated hemoglobin increased
Metabolism and Nutrition Disorders: anorexia, hypokalemia, hypothermia, hypoglycemia
Musculoskeletal and Connective Tissue Disorders: muscle tightness, rhabdomyolysis, mobility decreased
Nervous System Disorders: memory impairment, cogwheel rigidity, hypokinesia, myclonus, bradykinesia, akinesia, coordination abnormal, speech disorder, choreoathetosis
Psychiatric Disorders: aggression, loss of libido, delirium, libido increased, anorgasmia, tic, homicidal ideation, catatonia, sleep walking

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

Postmarketing Experience: The following adverse reactions have been identified during post-approval use of oral aripiprazole. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or to establish a causal relationship to drug exposure:

- Occurrences of allergic reaction (anaphylactic reaction, angioedema, laryngospasm, pruritus, urticaria, or oropharyngeal spasms), pathological gambling, hiccups, blood glucose fluctuation,桃花心木 crisis, and drug reaction with eosinophilia and systemic symptoms (DRESS)

DRUG INTERACTIONS

Drugs Having Clinically Important Interactions With ARISTADA

Table 4: Clinically Important Drug Interactions With ARISTADA

<table>
<thead>
<tr>
<th>Strong CYP3A4 Inhibitors and CYP2D6 Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Impact:</strong></td>
</tr>
<tr>
<td><strong>Intervention:</strong></td>
</tr>
<tr>
<td><strong>Examples:</strong></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Strong CYP3A4 Inducers</th>
</tr>
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<tbody>
<tr>
<td><strong>Clinical Impact:</strong></td>
</tr>
<tr>
<td><strong>Intervention:</strong></td>
</tr>
<tr>
<td><strong>Examples:</strong></td>
</tr>
</tbody>
</table>

Antihypertensive Drugs

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

**Intervention:** Monitor blood pressure and adjust dose accordingly.

**Examples:** carvedilol, lisinopril, prazosin

Benzbodiazepines

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

**Intervention:** Monitor sedation and blood pressure. Adjust dose accordingly.

**Example:** Lorazepam

USE IN SPECIFIC POPULATIONS

Pregnancy

**Pregnancy Exposure Registry:** There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ARISTADA during pregnancy. For more information, contact the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2398 or visit http://www.womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/1.

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

**Clinical Considerations:** Fetal/Neonatal Adverse Reactions: Extrapyramidal and/or withdrawal symptoms, including agitation, hyperreflexia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder have been reported in neonates who were exposed to antipsychotic drugs during the third trimester of pregnancy. These symptoms have varied in severity and have been monitored for up to 7 days after birth. Monitor neonates for extrapyramidal and/or withdrawal symptoms and manage symptoms appropriately. Some neonates recover within hours or days without specific treatment; others required prolonged hospitalization.

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

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

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

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

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

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

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

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

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

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

OVERDOSE

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

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

To report SUSPECTED ADVERSE REACTIONS, contact Alkermes, Inc. at 1-866-274-8253 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

PATIENT COUNSELING INFORMATION

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

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

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Improving Outcomes in Late-Life Schizophrenia

Nery A. Diaz, DO, FAPA; Laura Clarke, MD, DFAPA; and Claire Holderness, MD

Olde adults with schizophrenia include indivi-duals with both early- and late-onset ill-ness. A distinction based on age is not a separate diagnosis in the ICD or the DSM-5; how-ever, the International Late-Onset Schizophrenia Group has proposed subdividing the diagnosis of schizophrenia into distinct age groups.1 A listing of the 3 distinct age groups is found in Table 1.

We focus here on treatment strategies to improve the quality of life for both older adults who are aging with schizophrenia, and those who are first diag-nosed with schizophrenia after age 40 years.

Early-Onset Schizophrenia

Although patients diagnosed with early-onset schizophrenia (EOS) have an increased risk of pre-mature mortality when compared with the general population, more individuals diagnosed with schizophrenia are living longer. This increased longevity is due to improvements in treatments for schizophrenia and for co-occurring medical condi-tions, such as hypertension, tobacco use, diabetes mellitus, and hyperlipidemia.2

In our clinical experience, adults with EOS will often develop adverse effects in association with medications that are no longer effective as they age. Staying receptive to changes in the needs of the older patient, as well as to the challenges pre-sented for the family and caregivers, helps ensure the formulation of a treatment plan that is manage-able and sustainable in the community.

CASE STUDY 1

"Ms Kahn" is an African American woman, aged 63 years, who was diagnosed with schizophrenia dur-ing her adolescence. Her disease course is notable for prominent positive symptoms despite treatment with clozapine for more than 10 years. Her medical course is notable for chronic constipation complicated by paralytic ileus, severe tardive dyskinesia, and benign ethnic neutropenia. Her primary sup-port is her sister, who is also her health care proxy.

Ms Kahn recently experienced an episode of paralytic ileus, which required a medical admis-sion, followed by a psychiatric admission for a re-view of her medication regimen and a gastrointes-tinal consultation. An attempt was made to maintain Ms Kahn on clozapine because of her favorable response as compared with other atypical antipsy-chotics. Clozapine could be successfully main-tained, however, only with a complex bowel regi-men including osmotic diuretics, stool softeners, laxatives, gastric transit accelerators, and enemas. Subsequently, Ms Kahn’s sister reported the diffi-culty of maintaining this complex regimen, and family meetings were arranged with the patient and her multidisciplinary medical team that includ-ed her gastrointestinal specialist. Ultimately, clo- zapine was cross-tapered to aripiprazole, which she appears to tolerate.

This case illustrates the challenges of treating aging adults diagnosed with EOS. The importance of collaborative care among the treatment teams, the patient, their family, and caregivers cannot be over-emphasized. The case also illustrates the need for regular interdisciplinary communication when work-ing with older adults who are diagnosed with multiple medical comorbidities. Finally, it underscores the importance of parsimony in medication regimen for older patients, especially those with schizophrenia.1

Epidemiology

Epidemiology data for psychosis diag-nosed after age 40 years are sparse, although some esti-mates state that 20% to 25% of patients with schizophrenia had an onset of the disorder after age 40 years.4 The prevalence esti-mate for schizophrenia is 0.6% to 1.0% in individuals aged between 45 and 64 years, and 0.1% and 0.5% in individuals 65 years and older.4

Table 1. Subcategories From the International Late-Onset Schizophrenia Group

<table>
<thead>
<tr>
<th>Subcategory</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early-onset schizophrenia</td>
<td>Before age 40 years</td>
</tr>
<tr>
<td>Late-onset schizophrenia</td>
<td>Aged 40-60 years</td>
</tr>
<tr>
<td>Very late-onset schizophrenia</td>
<td>After age 60 years</td>
</tr>
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Table 2. Key Risk Factors for Developing LOS and VLOS

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>LOS</th>
<th>VLOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>moderate</td>
<td>strong</td>
</tr>
<tr>
<td>Family history</td>
<td>moderate</td>
<td>low</td>
</tr>
<tr>
<td>Negative symptoms</td>
<td>moderate</td>
<td>low</td>
</tr>
</tbody>
</table>

[Key: LOS, late-onset schizophrenia; VLOS, very late-onset schizophrenia.]

New-Onset After Age 40 Years

Delusions and hallucinations in patients 40 years or older are usually associated with co-occurring medical illness, cognitive impairment, inappropri-ate medications, and sensory deficits. When such illnesses are not contributing to the origin of new-onset psychosis, a diagnosis of late-onset schizophrenia (LOS) or very late-onset schizophrenia (VLOS) should be considered. A summary of key risk factors for developing LOS and VLOS is found in Table 2.3
CASE STUDY 2

“Ms Garcia,” a Hispanic woman aged 65 years, presented to the emergency department (ED) for sudden onset of strange thoughts and behaviors, accompanied by her husband. She had no personal or family history of psychiatric disorders, and was retired and the mother of 1 adult son. At home, she had been wandering aimlessly without eating or drinking for several days. Despite evidence to the contrary, Ms Garcia feared her son had been abducted.

In the ED, she was suspicious, irritable, and disheveled. Ms Garcia was admitted to the medical unit where an exhaustive workup, including blood tests, heavy metals panel, lumbar puncture, and brain imaging, did not suggest a contributing etiology. She was transferred to psychiatric care, where she was diagnosed with VLOS. Her symptoms responded well to a gradual titration of olanzapine 10 mg at bedtime. During her hospitalization, she responded favorably to group interventions focused on recreational activities, peer supports, social skills training, and cognitive-enhancing interventions.

Engagement with Ms Garcia’s family began in the ED and continued throughout her admission. Early contacts obtained collateral history and information on the patient’s level of daily functioning. As her admission progressed, family meetings provided psychoeducation about her diagnosis and treatment planning to encourage the engagement of her family as collaborators in her care. Particular attention was given to the family’s language preferences, cultural values, and spiritual beliefs, and how these might influence their understanding of her diagnosis and treatment plan. Ms Garcia was referred to a community adult recreational center where she enjoys participating with peers and staff in social activities and treatment groups. Working with the family and case manager, her treatment team continues to monitor her symptoms, providing regular cognitive and functional assessments of other possible etiologies for her psychosis, such as dementia.

This case illustrates the importance of a comprehensive history and medical workup for older adults to rule out secondary causes of psychosis prior to a diagnosis of VLOS. Determining the correct diagnosis is imperative to facilitate early intervention and treatment. This case also illustrates good clinical practice of obtaining collateral information while engaging with the patient and the family in a manner that is culturally sensitive. Finally, the case underscores the value of combining pharmacology with psychosocial interventions to sustain recovery while engaging the patient in postdischarge treatment by offering regular assessments. This case also underscores the importance of a comprehensive approach when developing treatment plans for older adults diagnosed with VLOS.

Clinical Evaluation

Privacy and communication are essential for a thorough clinical evaluation. Privacy is important because adults are concerned about discussing personal matters in the presence of their adult children and nonfamilial caregivers. Language barriers are bridged with translation services.

Adults with Disabilities

For older adults with disabilities, mobile apps are useful. Properly fitted eyeglasses and hearing aids in good working condition are essential. Patients who are deaf or hearing impaired necessitate specialized interpreter services.

Clinical Presentation

There are significant differences in the clinical presentations of EOS when compared with LOS and VLOS, which have fewer negative symptoms. Patients diagnosed with LOS and VLOS tend to have a more successful history of employment and of intimate relations when compared with those with EOS.

Hallucinations and Delusions

The persecutory delusions of LOS are notable for accusatory voices and persecutory third-person commentaries. These symptoms are unlike the paranoid delusions and persecutory beliefs common in VLOS. Table 3 lists some distinguishing features of the hallucinations and delusions that are common in other disorders.

Cognitive Features

Teasing out the cognitive symptoms associated with LOS and VLOS that are superimposed on an aging brain can be difficult. Older adults with schizophrenia have twice the likelihood of developing dementia when compared with healthy peers. For clinical presentations that are complex, a comprehensive neuropsychological battery of testing with brain imaging can be helpful to clarify the diagnosis.

Pharmacology Treatment

Initial interventions with older patients should begin with a review of all medications, including prescribed treatments, herbal remedies, and over-the-counter supplements. This review is important to identify possible drug-to-drug interactions and medications that are on the Beers Criteria for Potentially Inappropriate Use in Older Adults. Care should be taken to avoid the risks and hazards of polypharmacy.

Antipsychotics have long been established as the standard treatment in schizophrenia. That means the big challenge for the clinician is include balancing the risks and benefits of treatment. Part of the difficulties of making this assessment, however, is a relative lack of research and evidence for the use of antipsychotics in older adults diagnosed with LOS. Metabolic and physiological changes associated with aging predispose the patient to be more sensitive to adverse effects, such as anticholinergic symptoms, increased fall risk, arrhythmias, and QTc prolongation. In addition, concerns for increased risk of cerebrovascular events and mortality in elderly dementia patients with psychosis led to US Food and Drug Administration (FDA) black-box warnings on all antipsychotics. Expert consensus guidelines on the use of antipsychotic agents in older patients encourage the use of atypical antipsychotics at minimally effective dosage and using a slow titration.

Early extrapyramidal symptoms (EPS) and advancing age are known risk factors for tardive dyskinesia (TD), a condition associated with higher mortality in psychiatric patients. Monitoring for EPS and TD is imperative. The Abnormal Involuntary Movement Scale should be used to monitor symptoms and to rate their severity.

Once EPS is diagnosed, a reasonable first step is to lower the antipsychotic dosage while considering a switch to an antipsychotic with less risk of EPS. Caution should be used with the addition of agents that may increase anticholinergic load.

Once TD is diagnosed, continued treatment with antipsychotics should be reviewed, including whether to discontinue treatment, decrease the dosage, or switch to an antipsychotic with less dopamine blockade. FDA-approved medications for the treatment of TD, such as the selective vesicular monoamine transporter 2 inhibitors valbenazine and deutetrabenazine, should be considered, especially for patients for whom continued use of antipsychotics is indicated. Given that the cumulative duration of antipsychotic treatment increases the risk of TD, antipsychotic dosage adjustments should be routinely considered in the older adult.

Table 3. Hallucinations and Delusions

| LOS and VLOS. Persecutory delusions; partition delusions. The latter is the belief that people, objects, and gases can pass through barriers such as walls, floor, ceilings, and ventilation shafts. |
| Frontotemporal dementia. Hallucinations and delusions are rare. |
| Dementia with Lewy bodies. Visual hallucinations involving little people, fantasy figures, and animals. Often experienced by patients suffering from coexisting medical conditions, such as delirium, seizure disorders, brain tumors, and visual problems. |

[Key] LOS, late-onset schizophrenia; VLOS, very late-onset schizophrenia.
Psychosocial Interventions

In the older adult, the treatment plan should reflect an array of supports, ideally in an integrated care setting. Integrative care models have been shown to be effective for community-dwelling adults with severe mental illness, and efforts are being made to disseminate this collaborative approach on a global scale. Examples of other effective psychosocial interventions include family therapy, peer support, occupational therapy, cognitive behavioral therapy, cognitive remediation, and social skills training. Community resources, social programs, and support for caregivers are also known to promote and sustain recovery and to minimize the loneliness, isolation, and stigma associated with aging and a severe mental disorder.

Concluding Thoughts

Improving outcomes in late-life schizophrenia begins with a thorough medical evaluation to rule out secondary sources of psychosis. Ideally, treatment is patient-centered, culturally sensitive, and includes the judicious use of antipsychotics and psychosocial interventions.

More research is needed to understand the development of schizophrenia in late life. Initiatives to minimize the disease burden and improve the quality of life for older adults with schizophrenia and their families / caregivers are important. These interventions benefit society as a whole and should be a legislative priority.

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REFERENCES

Results From the Mental Status Exam
Roger was pleasant upon approach. He said he was glad he had sought admission and was “less lonely now.” He had a fresh-faced look, with good hygiene, and he maintained good eye contact. He said his mood was depressed: “a 7 or 8 on a scale of 1 to 10.”

The mental status exam was normal except for some difficulty with short-term memory. He scored 22 of 30 on the mini-mental state examination, which is consistent with mild cognitive impairment. On the Montreal Cognitive Assessment Test for Dementia, Roger scored 18 of 30, which is consistent with mild dementia. The score can be influenced by factors like fatigue or sedating medications. His long-term memory was adequate.

In ascertaining his substance use history, Roger said he was a social drinker but “had managed to stop entirely over the past year.” He also noted that, up until a year ago, he drank to help with his sleeping problem, saying he “would take a couple of shots of tequila or vodka to knock me out.” He felt this strategy was “necessary to cope.” He stopped alcohol use when he had memory issues and fell at home a few times.

Up until a year ago, he drank to help with his sleeping problem, saying he “would take a couple of shots of tequila or vodka to knock me out.”

Insomnia, however, was still an issue. He noted that he had tried over-the-counter sleep aids, which “did nothing for me.” He volunteered that he had experimented with mushrooms while in college, which he had enjoyed, but he denied using them since then. He denied using cannabis or any other street drugs. His urine toxicology on admission was negative.

The Inpatient Unit: The Triad Comes to Light
Basic admission bloodwork results were normal. Thyroid function tests were normal. Chest X-ray was negative.

Roger was initially placed on risperidone 1 mg po BID, benztropine 0.5 mg po BID, and bupropion 75 mg po daily. He was started on desyrel 50 mg po (qHS), as needed, for the insomnia, which he said helped him sleep. He participated in many activities and groups on the unit. He was observed chatting with peers in a friendly way.

To further explore the diagnostic differential, a neurology consult was completed. The neurologist found no physical explanation for the nystagmus and ataxic gait. He concluded that both symptoms were psychogenic.

Since Roger believed he had a computed tomography (CT) scan during a prior hospitalization without any reports of abnormalities, one was not immediately completed on admission. The team requested records for the 2 prior psychiatric hospitalizations and, to be thorough, ordered a CT scan.

Similarly, an ophthalmology consult was ordered. It revealed normal healthy eyes except for the vertical nystagmus.

This triad—the combination of an eye disorder (in this case, vertical nystagmus, but it could be another ocular disturbance); a broad-based, ataxic gait; and a context of memory decrease along with mood and psychotic symptoms—was suggestive of Wernicke encephalopathy (WE) or Korsakoff psychosis. Interestingly, this syndrome usually occurs in the context of heavy alcohol consumption, and Roger noted upon admission that he was merely a social drinker. Upon physical examination, he had no signs of chronic or advanced alcohol use, eg, broken facial capillaries (“gin blemishes”), palmar erythema, or jaundice. The liver function tests on his admission chemistry labs were elevated, but they were still within normal limits. While on the unit, he showed no signs of alcohol withdrawal.

To further explore the possibility of WE, the team chatted again with Roger about his alcohol use to ascertain more details. For instance, Roger now noted that for his long history of sleep issues, he had drunk “several glasses”—not shots—of vodka or tequila nightly since about the age of 22 or 23.” He was now 34. Clarification of the term “several” was also pursued. Roger explained that meant “4 or 5 regular glasses; it takes that much to calm me down so I can finally sleep. I drink a lot of coffee during the day.”

Roger also admitted that this was his nightly routine, not just an occasional thing. He denied ever having any blackouts or withdrawal tremors. He explained, “I’ve always had a high tolerance for booze. It runs in my family.” He did not share these insights regarding alcohol intake at the initial interview. He further noted, again, that he decided to stop drinking about a year ago: “I was forgetting too much stuff, oversleeping sometimes, falling at home. I didn’t want to get fired.” Roger said he “had stopped on his own,” without going to an inpatient detoxification or rehabilitation facility, and he denied any withdrawal seizures. He said he attended a few Alcoholics Anonymous meetings but did not like the vibe and stopped.

Mystery Solved—and a Treatment Plan
The head CT with contrast showed changes in the thalamus consistent with WE. There were abnormalities noted in the cerebellum consistent with ataxia. Perhaps the head CTs at the prior hospital had not been interpreted properly. We ordered a serum thiamine (vitamin B1) level, which showed that he was severely deficient in thiamine. Based on these new findings, the criteria for WE diagnosis were met.

His loss of appetite and eating habits suggested the possibility of other vitamin deficiencies. We tested for serum vitamin B12, and vitamin D; he was severely deficient in both. This may well have contributed to his depressed mood.

To correct these vitamin deficiencies, the patient was transferred to a medicine inpatient unit. He received an intravenous (IV) bolus infusion of thiamine 500 mg 3 times daily for 2 days, then 250 mg IV daily for 5 days. In addition, Roger was started on vitamin B12 injections and high-dose vitamin D tablets. Within about 2 weeks, all of his vitamin levels were restored to the normal range.

His vertical nystagmus stopped completely. His ataxic gait resolved. The depression lessened considerably, and his hallucinations ended.

Table 1. Testing and Assessment Options

<table>
<thead>
<tr>
<th>Testing and Assessment Options</th>
<th>Tests that can detect alcohol-related dementia and Korsakoff syndrome</th>
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<tbody>
<tr>
<td>Neuropsychological tests for alcohol-related cognitive impairment</td>
<td></td>
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<tr>
<td>Mini-Mental Status Examination</td>
<td>Cambridge Cognitive Examination</td>
</tr>
<tr>
<td>Dementia Rating Scale</td>
<td>Three Words–Three Shapes</td>
</tr>
<tr>
<td>Montreal Cognitive Assessment</td>
<td>California Verbal Learning Test</td>
</tr>
<tr>
<td>Addenbrooke’s Cognitive Examination</td>
<td>Free and Cued Selective Reminding Test</td>
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www.psychiatrictimes.com
Roger was discharged on the same psychotherapy medications that he received as an inpatient: bupropion, 75 mg po qAM; risperidone, 1 mg po BID; benzotropine, 0.5 mg po BID; and desyrel, 50 mg po qHS as needed for insomnia. He was also prescribed vitamin supplements of thiamine, vitamin B12, and vitamin D, as well as a therapeutic multivitamin. Finally, he received a consult with a nutritionist to address his eating habits and was referred for supportive psychotherapy to help address his depression and family issues.

Exploring WE and Korsakoff Psychosis

In general, WE is reversible with thiamine infusions. However, failure to diagnose WE can lead to a serious amnestic syndrome (Korsakoff syndrome). Korsakoff psychosis is generally irreversible. Therefore, it is extremely important that patients are diagnosed and treated as promptly as possible.4,5

When a patient admits to social drinking, it is helpful to pinpoint the exact extent of alcohol use in terms of type of alcohol, quantity, and frequency.1 An assessment of a patient’s eating habits and nutritional intake (or lack thereof) can also contribute to the diagnosis and treatment of common psychiatric disorders.

A variety of evidence-based cognitive rating scales exist for WE.7 Heirene et al compared the neuropsychological tests used to assess alcohol-related cognitive impairment with tests that screen for alcohol-related dementia and Korsakoff syndrome (Table 1). They concluded that there is a heterogeneity in presentation and suggested using the more broad and inclusive diagnostic conceptualizations of alcohol-related cognitive impairment instead of the discrete diagnoses of Korsakoff syndrome and alcohol-related dementia.

Meanwhile, Sgouros et al has pursued the development of a Thiamine Deficiency Questionnaire (TDQ) to assess thiamine deficiency in patients with severe alcohol dependence.4 Unfortunately, they concluded that further refinement and evaluation were needed before endorsing TDQ’s validity.

Discussion

Alcohol use (as well as the use of other nonprescribed drugs) is often underreported by patients.4,6 Population surveys typically produce underestimates of alcohol consumption of approximately 40% to 50%.6,7 Thus, it is essential in the initial patient interview to receive answers that are as specific as possible regarding what kind of alcohol is being consumed, how much is consumed in a drinking session, and how often the sessions occur. If the patient admits to “a couple of beers,” ask if those are 12-ounce, 16-ounce, or 24-ounce drinks. Ask about the drinking pattern: Do they drink more on weekends than on weeknights when they have to get to work the next day? Listen for words like lonely, isolated, homesick, bored, trouble sleeping, frustration, and anger, as these can be common triggers for high levels of alcohol consumption.

Alcohol use disorder is not the only cause of WE; the culprit can be any condition that compromises the body’s access to vitamin B1 (thiamine) (Table 2).4,11 But those are cases for another day. This one is closed.

Dr Mausner is a board-certified psychiatrist. She is on the staff of Manhattan Psychiatric Center and works in its mental health outpatient clinic. Her new book Jacob Weinberg, Musical Pioneer is available on Amazon.com.

REFERENCES

n this PsychView custom video, Sanjay Rao, MD, and Kimberly Garcia, DNP, discuss their experience with long-acting injectable antipsychotics (LAIA) for schizophrenia. This article summarizes their conversation about the increasing role of LAIAs as an effective treatment choice in individuals with schizophrenia.

Garcia and Rao concurred that 10 to 15 years ago, LAIAs were prescribed in cases of frequently relapsing nonadherence, viewed as almost a punitive intervention. Now, both clinicians consider and recommend LAIAs much earlier in treatment. Rao pointed to the third edition of the American Psychiatric Association’s Practice Guideline for the Treatment of Patients With Schizophrenia, updated and published in 2021, which now recommends that a patient may be treated with a LAIA “if the patient prefers to receive an LAIA,” and LAIAs are also suggested for patients who have a history of uncertain or poor adherence.

A common theme throughout the presentation was the value of providing ongoing education to the patient and their support system so the patient can make the determination based on risks and benefits if an LAIA is the right choice for them.

Currently, they noted LAIAs are FDA approved to be dosed every 2, 6, or 8 weeks; every month; every 3 months, and most recently, every 6 months. Garcia shared her surprise that when patients have transitioned from a monthly injection to every 3 months, many prefer to continue monthly office visits, which allows more time to discuss other treatment issues. The flexibility of extended periods of time between doses of a LAIA also proved to be a clinical advantage during the COVID-19 pandemic, when care was delivered virtually. Like telehealth, this pandemic-driven treatment modification has become the preferred dosing schedule of some patients.

Rao highlighted the importance of understanding the differing initiation regimens for each of the LAIAs in use. He further explained that the initiation of some agents require “oral overlap for a few weeks. And for the newer ones, it typically means you have to give them 2 injections—either in rapid succession or over the course of a few days.” Significantly, for the LAIAs given at 3- and 6-month intervals, the patient must first achieve steady state by receiving 4 monthly injections of that drug.

Garcia and Rao agreed that depending on the treatment setting, prescribers’ understanding and comfort level with LAIAs, and state formularies, there remain varying degrees of system and clinician resistance. In the worst-case scenario, this resistance colludes with patient resistance, and LAIAs become dismissed as an option. Both clinicians noted some colleagues have maintained that patients were simply not interested in LAIAs. However, after they were educated on presenting the risks and benefits in an objective and informative manner, many ultimately chose an LAIA.

### Concluding Thoughts

One of the important pillars of treatment and relapse prevention is steady-state therapeutic antipsychotic medication levels. LAIAs provide a treatment option to help achieve this goal. Currently, the biggest challenge is to educate patients, patient support systems, prescribers, and mental health treatment teams about the risks and benefits of LAIAs in an objective and sincere manner.

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Dr Rao is a clinical professor of psychiatry at the University of California, San Diego. Dr Rao is a consultant for Alkermes, Janssen Pharmaceuticals; Speakers’ Bureau: Alkermes, Neurocrine Biosciences, Janssen Pharmaceuticals, Otsuka Pharmaceutical Co, Sunovion Pharmaceuticals.

Ms Garcia is an assistant clinical professor at the College of Nursing and Health Professions at Drexel University in Philadelphia, Pennsylvania.

### Table. LAIA Benefits

<table>
<thead>
<tr>
<th>Benefit</th>
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<tbody>
<tr>
<td>Convenience of infrequent dosing</td>
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<tr>
<td>Advantage of structure</td>
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<td>Privacy of antipsychotic use</td>
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<td>A possibility for those with difficulty accessing a pharmacy</td>
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<tr>
<td>Works well for those in an unstable living situation or are unhoused</td>
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<tr>
<td>Helpful for those who travel a lot</td>
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TMS: A Useful Clinical Tool for Treatment-Resistant Depression

Abhijit Ramanujam, MD

Developed in 1985 and approved by the US Food and Drug Administration in 2008, transcranial magnetic stimulation (TMS) technology has been gaining clinical interest as an effective treatment option for patients with treatment-resistant depression. Two-thirds of TMS patients experienced either full remission of their depression symptoms or noticeable improvements. TMS is a noninvasive outpatient procedure without serious adverse effects, making it an attractive option for patients who have not found relief from other treatments, including psychopharmacology and psychotherapy.

How TMS Works
TMS uses an alternating current passed through a metal coil placed against the scalp to generate rapidly alternating magnetic fields. These pass through the skull nearly unimpeded and induce electric currents that depolarize neurons in a focal area of the surface cortex.

The magnetic field generated by TMS is comparable to that of a standard magnetic resonance imaging device (MRI), measured at approximately 1.5 to 3 Teslas. However, the TMS field is focal (beneath the coil), whereas the MRI field is large and fills the room housing the MRI device.

One hypothesis on how TMS works is that the stimulation of discrete cortical regions alters pathologic activity within a network of gray matter brain regions, specifically those involved in mood regulation and connected to the targeted cortical sites. Functional imaging studies support this hypothesis by showing TMS can change activity in brain regions remote from the site of stimulation.

TMS has many molecular effects comparable to electroconvulsive therapy (ECT), including increased monoamine turnover and normalization of the hypothalamic pituitary axis. However, unlike ECT, TMS does not require general anesthesia and is not associated with impaired cognition. Additionally, in one neuroimaging study of depressed patients, a prefrontal serotonin deficiency at baseline normalized after treatment with TMS.

High-frequency stimulation is thought to excite the targeted neurons and is typically used to activate the left prefrontal cortex. Low-frequency stimulation appears to inhibit cortical activity and is usually directed at the right prefrontal cortex.

Consistent with this hypothesis, a review examined 66 studies in patients with depression who were treated with TMS targeting the dorsolateral prefrontal cortex. It found that high-frequency TMS generally increased regional cerebral blood flow, whereas low-frequency TMS generally decreased regional cerebral blood flow, which is reduced in a depressed brain.

When Is TMS a Good Option?
TMS is indicated for patients with unipolar major depression who have failed at least 1 antidepressant medication. In addition, TMS is indicated for patients who responded to a prior course of TMS. Its use for these patients is consistent with treatment guidelines from the American Psychiatric Association, Canadian Network for Mood and Anxiety Treatments, and the Royal Australian and New Zealand College of Psychiatrists.

The patient evaluation should confirm the primary diagnosis of treatment-resistant depression and determine whether the TMS intervention can be used safely. The assessment includes examinations of psychiatric history, general medical history, physical health, and mental status with emphasis upon depressive symptoms. This should emphasize risk factors for seizures and preexisting neurologic disease, such as epilepsy, intracranial masses, and vascular abnormalities.

TMS is contraindicated in patients with: increased risks for seizures, implanted metallic hardware (aneurysm clips, bullet fragments, etc), cochlear implants, implanted electrical devices (pacemakers, intracardiac lines, medication pumps, etc), and unstable general medical disorders. The Figure shares a 12-item questionnaire to determine if a patient is a good TMS candidate.

How Effective Is TMS?
Multiple reviews have found consistent evidence that TMS provides a clinically relevant benefit to patients with treatment-resistant depression. In patients with acute major depression who have not responded to at least 1 antidepressant medication, numerous meta-analyses of randomized trials have found TMS superior to placebo treatment.

A meta-analysis of 34 randomized trials compared TMS with placebo treatment in 1383 patients with treatment-resistant major depression. It found that improvement was greater with active treatment.

Add-on treatment with TMS was efficacious in patients who had not responded to an adequate antidepressant therapy. Response (for example, the reduction of baseline symptoms ≥ 50%) occurred in more patients who received active (47%) versus placebo (22%) TMS.

There have been no consistent predictors of response according to a meta-analyses. A 1-year, prospective observational study of 120 patients who responded or remitted with acute TMS found that the durability of response to TMS was not associated with age, sex, severity of depressive symptoms prior to TMS, nor the number of failed antidepressant trials prior to TMS.

For treatment of major depression, TMS is less efficacious than ECT. Follow-up studies of patients with major depression who were treated acutely with TMS in randomized trials indicate that the short-term benefits of TMS are stable.

With regard to longer-term benefits of TMS, prospective, observational studies lasting at least 6 months suggest that in patients with major de-
prescription who improve with acute TMS, relapse occurs in about 35%.14
For patients with unipolar major depression who improve with a course of TMS and subse-
quently deteriorate or relapse, reintroduction of TMS using the same stimulation parameters may be
helpful.14 It is not known if maintenance treat-
ment with TMS for unipolar major depression is beneficical, as few randomized trials using stan-
dard protocols have been conducted. However, in several, observational studies of patients, the
results suggest that maintenance TMS may, perhaps, be beneficical.15
How Safe Is TMS?
TMS is generally safe and well-tolerated. For ex-
ample, in a randomized trial of 301 patients, in-
vestigators found that study discontinuation due
to adverse effects was comparable for active and
placebo TMS (5% and 3%, respectively).17
The most serious adverse effect of TMS is a
generalized tonic-clonic seizure. However, the risk
of seizure appears to be comparable to that for
anti depressant medications. Seizures probably occur
in less than 0.1 to 0.5% of patients when safety
guidelines are followed regarding patient selection
and stimulation parameters. Seizures that have oc-
curred were self-limited, required no medications,
and did not recur.15 Factors that increase the risk
of seizures can be found in the Table.
Other effects include hypomania and mania,
described in randomized trials18 and reports of
patients with major depression (both unipolar and
bipolar) who were treated with TMS.16
However, the clinical significance is not
known, because patients with bipolar major de-
pression can switch to mood-elevated states in
the absence of an antidepressant treatment. Treatment
of unipolar major depression with TMS does not
appear to increase suicidal ideation or behavior.15
What About Side Effects?
HEADACHE AND SCALP PAIN. A review of randomized
trials in patients with major depression found that
the incidence of headache with active treatment
and placebo treatment was 28% and 16%, respec-
tively. The incidence of scalp pain with active and
placebo treatment was 39% and 15%, respec-
tively. No migraine headaches have been re-
ported. Headache and scalp pain may be more
pronounced when higher stimulation frequencies and
intensities are used. Topical lidocaine may
reduce scalp pain. Reducing stimulation intensity
can decrease scalp discomfort, but this can also
reduce efficacy of treatment. For sensitive pa-
tients, the dose of TMS can be titrated up during
the first week. Headache and scalp pain generally
resolve over the first 2 weeks, although some pa-
tients may require an analgesic, such as acetamin-
ophen or ibuprofen.22
TRANSIENT (< 4 HOURS) INCREASE IN AUDITORY
THRESHOLD. This is caused by repeated clicks that are
produced as current passes through the stimu-
lating magnetic coil and mechanically deforms
the coil. Hearing loss is prevented with foam ear-
plugs or noise protection ear coverings.
VasoVagal syncope. Management generally con-
sists of reassurance.
Special Concerns
ELDERLY. For older patients with major depression,
TMS can be beneficial if the stimulation intensity is
sufficient.23 Prefrontal atrophy in older patients can
increase the distance between the coil and
cortex to the point that lower-intensity stimula-
tion, which typically penetrates to a depth of 2 to
3 cm, does not affect cortical activity. Increasing
the intensity above the motor threshold can over-
come the added distance.17
PostSTROKer DepressIOn. Depression frequently oc-
curs after stroke, and TMS may help these patients.
Pregnancy and Postpartum Depression. For these
patients with major depression, observational studies suggest that TMS may possibly be safe
and effective. It appears unlikely that the fetus is
directly affected by TMS because magnetic fields
rapidly attenuate with distance.17
Concluding Thoughts
TMS is an exciting and promising therapy that can
provide real and lasting relief for patients with
outpatient-resistant depression. Conducted in an
outpatient setting, TMS is a noninvasive procedure
that is generally safe and well-tolerated. This
provides patients with the flexibility to seek treatment
in a way that does not disrupt their daily lives.
TMS has an equally promising future, with studies
exploring its expanded applications, as well as its
use as an ongoing maintenance treatment.
Dr Ramanujam is a psychiatrist and regional
medical director at Community Psychiatry +
MindPath Care Centers.

Table. Factors That Increase Risk of
Seizure
- Patient factors, such as medications, blood alcohol concentration, schizophrenia, and a history of head injury
- Personal and family (parent, sibling, or child) history of epilepsy
- Preexisting neurological disorder (for example, prior head injury with loss of consciousness, prior brain surgery, or congenital brain malformation)
- Medications that lower seizure threshold (bupropion, stimulants, tricyclic antidepressants, antipsychotics, and theophylline, etc.)
- Recent discontinuation of alcohol, benzodiazepines, or anticonvulsants
- Sleep deprivation
- TMS stimulation parameters
- Higher frequency
- Increased intensity
- Shorter intertrain interval

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INDICATION AND LIMITATIONS OF USE

Vyvanse is indicated for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in adults and pediatric patients 6 and older. Pediatric patients with ADHD younger than 6 years of age experienced more long-term weight loss than patients 6 years and older. Vyvanse is not indicated or recommended for weight loss. Use of other sympathomimetic drugs for weight loss has been associated with serious cardiovascular adverse events. The safety and effectiveness of Vyvanse for the treatment of obesity have not been established.

CONTRAINDICATIONS

- Use with monoamine oxidase inhibitors (MAOIs) or within
- Contraindications
- Known hypersensitivity to amphetamines or other
- Use with monoamine oxidase inhibitors (MAOIs) or within
- Warnings and Precautions
- Prior to and during treatment assess for the presence of
- CNS stimulants cause increases in blood pressure (mean increase about 2-4 mm Hg) and heart rate (mean increase about 3-6 bpm). Monitor all patients for tachycardia and hypertension.
- Exacerbation of Pre-existing Psychosis: May exacerbate symptoms of behavior disturbance and thought disorder in patients with a pre-existing psychotic disorder. Induction of a Manic Episode in Patients with Bipolar Disorder: May induce a mixed/manic episode in patients with bipolar disorder. Prior to initiating treatment, screen for risk factors for developing a manic episode (e.g., comorbid or history of depressive symptoms, or a family history of suicide, bipolar disorder, and depression). New Psychotic or Manic Symptoms: At recommended doses, may cause psychotic or manic symptoms (e.g., hallucinations, delusional thinking, or mania) in patients with no prior history of psychotic illness or mania. Discontinue if symptoms occur.
- CNS stimulants have been associated with weight loss and slowing of growth rate in pediatric patients (monitor weight and height). Treatment may need to be interrupted in patients not growing or gaining weight as expected. Vyvanse is not approved for use in pediatric patients below 6 years of age.

WARNING: ABUSE AND DEPENDENCE

- CNS stimulants, including Vyvanse, other amphetamine-containing products, and methylphenidate have
- Contraindications
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IMPORTANT SAFETY INFORMATION

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Vyvanse demonstrated significant improvement in attention in adults with ADHD.

Learn more at VyvansePro.com/Start
**VYVANSE (LISDEXAMFETAMINE DIMESYLATE) DEMONSTRATED SIGNIFICANT IMPROVEMENT IN ATTENTION IN ADULTS WITH ADHD**

**Primary Endpoint:** Average of the PERMP* total scores from all postdose sessions measured, from 2 to 14 hours.1,2

**STUDY DESIGN**
Multicenter, randomized, double-blind, placebo-controlled, crossover, modified analog classroom study to simulate a workplace environment in 142 adults aged 18-55 years with ADHD (as defined by Diagnostic and Statistical Manual of Mental Disorders, 4th ed., text revision)1,2

During a 4-week, open-label, dose optimization phase, subjects were titrated to an optimal dose of Vyvanse 30, 50, or 70 mg/day in the morning. They were then randomized in the double-blind crossover phase to receive Vyvanse (optimized dose) followed by placebo or placebo followed by Vyvanse, each for 1 week. During the double-blind phase, efficacy assessments occurred at the end of each week using PERMP1,2

*PERMP is an objective, validated, skill-adjusted math test that measures attention in ADHD. The PERMP total score comprises the sum of the number of math problems attempted and the number of math problems answered correctly. Higher scores indicate less severe symptoms. PERMP is not a test of the ability to learn math. PERMP conducted at 2, 4, 8, 10, 12, and 14 hours postdose.

PERMP=Permanent Product Measure of Performance.

The three core symptoms of ADHD are inattention, hyperactivity, and impulsivity. Symptoms must occur often and appear in two or more settings. Diagnosis should be based on a complete patient history and full clinical evaluation based on the DSM-5.

*Adverse Reactions (continued)*
- Adults: decreased appetite, insomnia, dry mouth, diarrhea, nausea, anxiety, and anorexia.

**Pregnancy and Lactation**
Vyvanse may cause fetal harm. Breastfeeding is not recommended during Vyvanse treatment.

**Please see accompanying Full Prescribing Information on following pages.**

References:
BRIEF SUMMARY: Consult the Full Prescribing Information for complete product information.

WARNING: ABUSE AND DEPENDENCE

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

CONTRAINDICATIONS

VYVANSE is contraindicated in patients with:

- Known hypersensitivity to amphetamine products or other ingredients of VYVANSE. Anaphylactic reactions, Stevens-Johnson Syndrome, angioedema, and urticaria have been observed in postmarketing reports.
- Patients taking monoamine oxidase inhibitors (MAOIs), or within 14 days of stopping MAOIs (including MAOIs such as linezolid or intravenous methylene blue), because of an increased risk of hypertensive crisis.

WARNINGS AND PRECAUTIONS

Potential for Abuse and Dependence (See Above)

Serious Cardiovascular Reactions

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

Blood Pressure and Heart Rate Increases

CNS stimulants cause an increase in blood pressure (mean increase about 2 to 4 mm Hg) and heart rate (mean increase about 3 to 6 bpm). Monitor all patients for potential tachycardia and hypertension.

Psychiatric Adverse Reactions

Exacerbation of Pre-existing Psychosis

CNS stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a pre-existing psychotic disorder.

Induction of a Manic Episode in Patients with Bipolar Disorder

CNS stimulants may induce a mixed/manic episode in patients with bipolar disorder. Prior to initiating treatment, screen patients for risk factors for developing a manic episode (e.g., comorbid or history of depressive symptoms or a family history of suicide, bipolar disorder, and depression).

New Psychotic or Manic Symptoms

CNS stimulants, at recommended doses, may cause psychotic or manic symptoms (e.g., hallucinations, delusional thinking, or mania) in patients without a prior history of psychotic illness or mania. If such symptoms occur, consider discontinuing VYVANSE. In a pooled analysis of multiple short-term, placebo-controlled studies of CNS stimulants, psychotic or manic symptoms occurred in 0.1% of CNS stimulant-treated patients compared to 0% in placebo-treated patients.

Suppression of Growth

CNS stimulants have been associated with weight loss and slowing of growth rate in pediatric patients. Closely monitor growth (weight and height) in pediatric patients treated with CNS stimulants, including VYVANSE. In a 4-week, placebo-controlled trial of VYVANSE in patients ages 6 to 12 years old with ADHD, there was a dose-related decrease in weight in the VYVANSE groups compared to weight gain in the placebo group. Additionally, in studies of another CNS stimulant, there was a slowing of the increase in height. Patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted. VYVANSE is not approved for use in pediatric patients below 6 years of age.

Peripheral Vasculopathy, including Raynaud’s Phenomenon

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

Serootonin Syndrome

Serootonin syndrome, a potentially life-threatening reaction, may occur when amphetamines are used in combination with other drugs that affect the serotonin or norepinephrine transporter systems such as monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John’s Wort. The co-administration with cytochrome P450 2D6 (CYP2D6) inhibitors may also increase the risk with increased exposure to the active metabolite of VYVANSE (d-amphetamine). In these situations, consider an alternative non-serotonergic drug or an alternative drug that does not inhibit CYP2D6. Serootonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Concomitant use of VYVANSE with MAO drugs is contraindicated.

Discontinue treatment with VYVANSE and any concomitant serotonergic agents immediately if symptoms of serotonin syndrome occur, and initiate supportive symptomatic treatment. If concomitant use of VYVANSE with other serotonergic drugs or CYP2D6 inhibitors is clinically warranted, initiate VYVANSE with lower doses, monitor patients for the emergence of serotonin syndrome during drug initiation or titration, and inform patients of the increased risk for serotonin syndrome.

ADVERSE REACTIONS

Clinical Trial Experience

Based on data from 4-week parallel-group controlled clinical studies of VYVANSE in pediatric and adult patients with ADHD.

Adverse Reactions Associated with Discontinuation of Treatment

In the controlled trial in pediatric patients ages 6 to 12 years, 8% (18/218) of VYVANSE-treated patients discontinued due to adverse reactions compared to 0% (0/72) of placebo-treated patients. The most frequently reported adverse reactions leading to discontinuation (1% or more and twice rate of placebo) were insomnia (8/358; 2%), tachycardia (3/358; 1%), irritability (2/358; 1%), hypertension (4/358; 1%), headache (2/358; 1%), anxiety (2/358; 1%), and dyspnea (3/358; 1%).

Adverse Reactions Occurring at an Incidence of ≥5% or More Among VYVANSE Treated Patients with ADHD in Clinical Trials

Most common adverse reactions (incidence ≥5% and at a rate at least twice placebo) reported in pediatric patients ages 6 to 12 years, and/or adults were anorexia, anxiety, decreased appetite, decreased weight, diarrhea, dizziness, dry mouth, irritability, insomnia, nausea, upper abdominal pain, and vomiting.

Adverse Reactions Occurring at an Incidence of ≥2% or More Among VYVANSE Treated Patients with ADHD in Clinical Trials

Adverse reactions reported in the controlled trials in pediatric patients ages 6 to 12 years, pediatric patients ages 13 to 17 years, and adult patients treated with VYVANSE or placebo:

- Adverse Reactions Reported by ≥2% of Pediatric Patients Ages 6 to 12 Years with ADHD Taking VYVANSE and Greater than or Equal to Twice the Incidence in Patients Taking Placebo - VYVANSE (n=218), Placebo (n=72):
  - Decreased Appetite (39%, 4%), Insomnia (22%, 3%), Abdominal Pain Upper (12%, 6%), Irritability (10%, 0%), Vomiting (9%, 4%) Weight Decreased (9%, 1%), Nausea (6%, 3%), Dry Mouth (5%, 0%), Dizziness (5%, 0%), Affect lability (3%, 0%), Rash (3%, 0%), Pyrexia (2%, 1%), Somnolence (2%, 1%), Tic (2%, 0%), Anorexia (2%, 0%).

- Adverse Reactions Reported by ≥2% of Pediatric Patients Ages 13 to 17 Years with ADHD Taking VYVANSE and Greater than or Equal to Twice the Incidence in Patients Taking Placebo - VYVANSE (n=233), Placebo (n=77):
  - Decreased Appetite (34%, 3%), Insomnia (13%, 4%), Weight Decreased (9%, 0%), Dry Mouth (4%, 1%), Palpitations (2%, 1%), Anorexia (2%, 0%), Tremor (2%, 0%).

- Adverse Reactions Reported by ≥2% of Adult Patients with ADHD Taking VYVANSE and Greater than or Equal to Twice the Incidence in Patients Taking Placebo - VYVANSE (n=358), Placebo (n=62):

**Capsules 10, 20, 30, 40, 50, 60, 70 mg**

- Capsules 10, 20, 30, 40, 50, 60 mg CII Rx Only
Decreased Appetite (27%, 2%), Insomnia (27%, 8%), Dry Mouth (26%, 3%), Diarrhea (7%, 0%), Nausea (7%, 0%), Anxiety (6%, 0%), Anorexia (5%, 0%), Feeling Jittery (4%, 0%), Agitation (3%, 0%), Increased Blood Pressure (3%, 0%), Hyperhidrosis (3%, 0%), Restlessness (3%, 0%), Decreased Weight (5%, 0%), Dyspnea (2%, 0%), Increased Heart Rate (2%, 0%), Tremor (2%, 0%), Palpitations (2%, 0%).

In addition, in the adult population erectile dysfunction was observed in 2.6% of males on VYVANSE and 0% on placebo; decreased libido was observed in 1.4% of subjects on VYVANSE and 0% on placebo.

Postmarketing Experience
The following adverse reactions have been identified during postapproval use of VYVANSE. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events are as follows: cardiomyopathy, mydriasis, diplopia, difficulties with visual accommodation, blurred vision, eosinophilic hepatitis, anaphylactic reaction, hypersensitivity, dyskinesia, dysgeusia, tics, bruxism, depression, dermatillomania, alopecia, aggression, Stevens-Johnson Syndrome, chest pain, angioedema, urticaria, seizures, libido changes, frequent or prolonged erections, constipation, and rhabdomyolysis.

DRUG INTERACTIONS
Clinically Important Interactions with Amphetamines

MAO Inhibitors (MAOI)
Clinical Impact: MAOI antidepressants slow amphetamine metabolism, increasing amphetamines effect on the release of norepinephrine and other monoamines from adrenergic nerve endings causing headaches and other signs of hypertensive crisis. Toxic neurological effects and malignant hyperpyrexia can occur, sometimes with fatal results.

Intervention: Do not administer VYVANSE during or within 14 days following the administration of MAOI [see Contraindications].

Serotonergic Drugs
Clinical Impact: The concomitant use of VYVANSE and serotonergic drugs increases the risk of serotonin syndrome.

Intervention: Initiate with lower doses and monitor patients for signs and symptoms of serotonin syndrome, particularly during VYVANSE initiation or dosage increase. If serotonin syndrome occurs, discontinue VYVANSE and the concomitant serotonergic drug(s) [see Warnings and Precautions].

CYP2D6 Inhibitors
Clinical Impact: The concomitant use of VYVANSE and CYP2D6 inhibitors may increase the exposure of dextroamphetamine, the active metabolite of VYVANSE, compared to the use of the drug alone and increase the risk of serotonin syndrome.

Intervention: Initiate with lower doses and monitor patients for signs and symptoms of serotonin syndrome particularly during VYVANSE initiation and after a dosage increase. If serotonin syndrome occurs, discontinue VYVANSE and the CYP2D6 inhibitor [see Warnings and Precautions and Overdosage].

Alkalizing Agents
Clinical Impact: Urinary alkalizing agents can increase blood levels and potentiate the action of amphetamine.

Intervention: Co-administration of VYVANSE and urinary alkalizing agents should be avoided.

Acidifying Agents
Clinical Impact: Urinary acidifying agents can lower blood levels and efficacy of amphetamines.

Intervention: Increase dose based on clinical response.

Tricyclic Antidepressants
Clinical Impact: May enhance the activity of tricyclic or sympathomimetic agents causing striking and sustained increases in the concentration of d-amphetamine in the brain; cardiovascular effects can be potentiated.

Intervention: Monitor frequently and adjust or use alternative therapy based on clinical response.

Drugs Having No Clinically Important Interactions with VYVANSE
From a pharmacokinetic perspective, no dose adjustment of VYVANSE is necessary when VYVANSE is co-administered with guanfacine, venlafaxine, or omeprazole. In addition, no dose adjustment of guanfacine or venlafaxine is needed when VYVANSE is co-administered.

From a pharmacokinetic perspective, no dose adjustment for drugs that are substrates of CYP1A2 (e.g. theophylline, duloxetine, melatonin), CYP2D6 (e.g. atomoxetine, desipramine, venlafaxine), CYP2C19 (e.g. omeprazole, lansoprazole, clozabam), and CYP3A4 (e.g. midazolam, pimozide, simvastatin) is necessary when VYVANSE is co-administered.

USE IN SPECIFIC POPULATIONS
Pregnancy
Pregnancy Exposure Registry
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ADHD medications during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Psychostimulants at 1-866-961-2388 or visiting online at https://womensmentalhealth.org/clinical-and-researchprograms/pregnancyregistry/adhd-medications/.

Risk Summary
The limited available data from published literature and postmarketing reports on use of VYVANSE in pregnant women are not sufficient to inform a drug-associated risk for major birth defects and miscarriage. Adverse pregnancy outcomes, including premature delivery and low birth weight, have been seen in infants born to mothers dependent on amphetamines. Monitor infants born to mothers taking amphetamines for symptoms of withdrawal such as feeding difficulties, irritability, agitation, and excessive drowsiness.

Lactation
Lisdexamfetamine is a pro-drug of dextroamphetamine. Based on limited case reports in published literature, amphetamine (d-or d,-)- is present in human milk, at relative infant doses of 2% to 13.8% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 1.9 and 7.5. There are no reports of adverse effects on the breastfed infant. Long-term neuromodulatory effects on infants from amphetamine exposure are unknown. It is possible that large dosages of dextroamphetamine might interfere with milk production, especially in women whose lactation is not well established. Because of the potential for serious adverse reactions in nursing infants, including serious cardiovascular reactions, blood pressure and heart rate increase, suppression of growth, and peripheral vasculopathy, advise patients that breastfeeding is not recommended during treatment with VYVANSE.

Pediatric Use
Safety and effectiveness of VYVANSE have not been established in pediatric patients below the age of 6 years.

Geriatric Use
Clinical studies of VYVANSE did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Renal Impairment
Due to reduced clearance in patients with severe renal impairment (GFR 15 to <30 mL/min/1.73 m2), the maximum dose should not exceed 50 mg/day. The maximum recommended dose in ESRD (GFR <15 mL/min/1.73 m2) patients is 30 mg/day.

Lisdexamfetamine and d-amphetamine are not dialyzable.

DRUG ABUSE AND DEPENDENCE
VYVANSE contains lisdexamfetamine, a prodrug of amphetamine, a Schedule II controlled substance.

OVERDOSAGE
Consult with a Certified Poison Control Center (1-800-222-1222) for up-to-date guidance and advice for treatment of overdose. Individual patient response to amphetamines varies widely. Toxic symptoms may occur idiosyncratically at low doses. Manifestations of amphetamine overdose include restlessness, tremor, hyperreflexia, rapid respiration, confusion, hallucinations, panic states, hyperpyrexia, and rhabdomyolysis. Fatigue and depression usually follow the central nervous system stimulation. Serotonin syndrome has been reported with amphetamine use, including VYVANSE. Other reactions include arrhythmias, hypertension or hypotension, circulatory collapse, nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning is usually preceded by convulsions and coma.

Lisdexamfetamine and d-amphetamine are not dialyzable.

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For more information, go to www.VYVANSE.com or call 1-877-TAKEDA-7 (1-877-825-3327).

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US Pat No. 7,105,486, 7,233,735, 7,655,630, 7,659,253, 7,659,254, 7,662,787, 7,662,788, 7,671,030, 7,671,031, 7,674,774, 7,678,770, 7,678,771, 7,687,466, 7,687,467, 7,713,936, 7,718,619, 7,723,305

Last Modified: 10/2021 US-LIS-1188v1.0 10/21
Benzodiazepines: Opiates That Evoke a Visceral Reaction

**Leah Kuntz**

“Benzodiazepines. Is there any class of medications probably other than opiates that evokes that same visceral reaction? I don’t think so,” said Jeffrey R. Strawn, MD.

Strawn playfully asked the audience, “How many of you are like me—you have that love-hate relationship with the benzodiazepines?” About 90% of the in-person audience raised their hands.

To begin, Strawn discussed the advantages and disadvantages of benzodiazepine use. Advantages include rapid onset, reasonable tolerability, usefulness for breakthrough symptoms, and possible usefulness for acute and chronic anxiety. Disadvantages include initial sedation, memory impairment, falls, possible increased risk of fracture, and possible abuse dependence and withdrawal.

According to Strawn, recent findings show that approximately 7.4% of patients seen in psychiatric care are receiving benzodiazepines. Unfortunately, the agents are misused by 5.2 million adults, of whom 0.5 million have benzodiazepine use disorder and 0.3 million have benzodiazepine dependence. Factors that increase risk of misuse, use disorders, and harms include younger age, male gender, socioeconomic disadvantage, and current or history of substance use disorders, as well as being divorced, separated, or never married.

Despite these issues, Strawn said, “Benzodiazepines have a role in treating anxiety disorders, but they require monitoring and consideration of risks/benefits.”

Tolerance data are mixed, although benzodiazepines should be used carefully in patients who have a history of substance use. The agents could be beneficial when a patient has breakthrough symptoms, rapid onset is needed (eg, for panic attacks), or a patient is experiencing acute expected anxiety (eg, phobias). However, older patients and children, as well as those who concurrently use opioids, have a history of substance use disorder, are at risk of falling, or operate heavy machinery, should be carefully monitored because they the risk-benefit ratio is not as strong.

**REFERENCES**


Managing the 4 Most Common Adverse Effects of Antipsychotics

**Erin O’Brien**

Andrew J. Cutler, MD, presented on the clinical management of the 4 most common adverse effects associated with antipsychotic medications that can negatively affect treatment adherence. In “Safety First: A Comparison of the Safety and Tolerability of Antipsychotics,” Cutler discussed these adverse effect—metabolic problems, movement disorders, sedation, and sexual dysfunction—as well as the treatment strategies medical providers can use to optimize the management of these adverse effects according to individual patient needs.

To manage metabolic problems, Cutler, who is clinical associate professor in the Department of Psychiatry at SUNY Upstate Medical University in Syracuse, New York, recommended monitoring metabolic parameters, weight gain, and appetite changes; encouraging a healthy diet and active lifestyle; choosing agents with lower incidence of weight gain when possible (eg, aripiprazole, olanzapine); considering the incorporation of metformin when initiating treatment with olanzapine or clozapine; or using olanzapine with samidorphan instead of olanzapine alone.

For movement disorders, he suggested some specific strategies for drug-induced Parkinsonism and akathisia, which both may be mitigated by reducing dosage or switching to medications with lower risk (eg, clozapine, iloperidone, lumateperone) when possible. Introducing adjunctive medications (eg, beta-adrenergic blockers, benzodiazepines) may also be helpful in cases of akathisia.

To address issues associated with sedation, Cutler recommended a few strategies, including consolidating antipsychotic medication doses into once-daily doses; identifying any potential interactions between the antipsychotics and other medications the patient may be taking; ruling out comorbid disorders that may be contributing to the sedation; and switching to antipsychotics with a lower risk of sedation (eg, lumateperone, pimavanserin) when possible.

Finally, when considering issues in sexual dysfunction, he suggested selecting an antipsychotic agent with lower likelihood of elevating prolactin (eg, lurasidone, quetiapine) or lowering prolactin (eg, brexpiprazole, cariprazine); considering adding low doses of aripiprazole to another antipsychotic that is causing sexual dysfunction; and incorporating psychosocial strategies such as relationship counseling and psychoeducation.

“Medications used to treat psychosis may be the single most powerful tool in a clinician’s armamentarium for reducing antipsychotic-induced AE’s,” said Cutler in his presentation.

Cutler is also the chief medical officer for NEI.

**REFERENCE**

Improving Patient Outcomes With Cultural Humility

**Erin O’Brien**

Napoleon B. Higgins Jr, MD, and Rona J. Hu, MD, presented on the impact of cultural differences and issues on health disparities and unequal access to care.

Higgins and Hu reported that countless incidents of racism and oppression have occurred over the years in mental health care. For instance, patients from minority communities have often been excluded from research studies; diagnostic assessments have not been sensitive for minority populations; diagnostic and treatment algorithms often pay little attention to diversity; and not as much is known about the differences in the ways individuals from different cultures may express symptoms of mental illness. Therefore, they concluded, patients from minority communities may distrust the medical system. This lack of information about—and trust from—these communities is problematic in part because racial and ethnic minority community members will increase by 90% by 2050, the United States Census Bureau predicts.

To improve outcomes with patients from minority communities, Higgins and Hu suggested that practitioners recognize their privilege and the historical role of privilege in oppressive systems. This includes examining their own biases and stereotypes, and the ways these impact reactions to microaggressions and other cultural issues in therapeutic settings.

They also advocated practicing cultural humility, which Higgins and Hu defined as a willingness and lifelong dedication to learn from patients about their experiences by asking questions, rather than making assumptions. “We don’t want to make assumptions—we always want to ask and be inquisitive,” Higgins said during the presentation. “When you show that you’re inquisitive, it shows interest, not ignorance. When you ask the question, it shows that you’re interested in that person’s story.”

Higgins is president and CEO of Bay Pointe Behavioral Health Service and South East Houston Research Group; executive director of Black Psychiatrists of America. Hu is a clinical professor in the Stanford Medical Center Department of Psychiatry and Behavioral Sciences.

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Looking for Comorbidities With ADHD From Day 1

**Leah Kuntz**

“It’s important that from day 1 we see the patient, we are looking for comorbidities,” said Napoleon B. Higgins Jr, MD, president and CEO of Bay Pointe Behavioral Health Services and South East Houston Research Group, medical director at Hold My Hand Residential Treatment Center, and executive director of Black Psychiatrists of America.

Higgins recommends considering the common comorbidities in the context of attention-deficit/hyperactivity disorder (ADHD) when planning treatment, and integrating treatment strategies that address both ADHD and comorbid conditions.

More than 50% of individuals with ADHD have comorbid disorders that may include learning and language disabilities, mood disorders (e.g., depression, mania), anxiety, anger and impulse control disorders, and tic disorders.

Child nutrition, Higgins stressed, is key: “When you have a child’s brain being developed on poor nutrition, you are going to have poor outcomes. You cannot have a Cheeto-derived brain.”

“Whatever helps the heart, helps the mind,” Higgins said of dietary behavioral interventions, parallel training, and making sure expectations are clear.

He also advocates for focusing on “the trump cards”—comorbid conditions that must be controlled before addressing ADHD, including mania, psychosis, depression, and learning disabilities.

Bipolar disorder and ADHD may be difficult to differentiate, Higgins noted. “I will say that the most common diagnosis that an adult with bipolar disorder will have if they were seen as a child is ADHD. Why is that?” he posed. “Mood issues tend to show up in later adolescence.”

He added, when transitioning to adulthood, children with ADHD must:

1. Take ownership of their treatment and direct the interview
2. Assist in finding a mental health provider
3. Transition from a child to an adult psychiatrist
4. Be screened for substance abuse
5. Schedule follow-ups during breaks in college
6. Focus outside of educational settings

Higgins said ADHD coaching can include: finding ways for the patient to decrease distractions; setting daily goals in manageable components; prioritize tasks with time-management strategies; and use a planning system, with a set place to work or study. Understanding their own emotions is also important, as is self-motivation or self-monitoring and, potentially, prayer and meditation.

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Beyond Culturally Competent Care for Transgender and Gender-Diverse People

**Leah Kuntz**

“I am not here to speak on behalf of the trans community. I do not presume to know their lived experience. What I do strive to do, however, is to infuse the lived experiences that they have entrusted with me into everything that I do, as a clinician, as a teacher, and as a researcher,” shared Rhonda Schwindt, DNP, RN, PMHNP-BC.

“Trans people have the right to determine who they are, and they have the right to expect that you will believe them. Now, in order to do that, we have to be willing to challenge that social construct that tells us gender can only exist within the binary male/female.”

Schwindt, an associate professor and director of the Psychiatric-Mental Health Nurse Practitioner Program at George Washington University School of Nursing in Ashburn, Virginia, told conference attendees.

To illustrate these issues, Schwindt discussed the case example of “Michael,” a 25-year-old who identifies as a transgender male. About 6 months prior to seeking assistance, Michael finally received a well-deserved and much-desired promotion; however, with the new role came a new office in a new building with new coworkers.

Almost immediately after assuming the position, Michael became the target of daily harassment, bullying, and discrimination. To avoid these interactions, Michael mapped out the nearest public restrooms, places where his coworkers could not judge him; shortly thereafter, he realized those bathroom trips were not sustainable so he began limiting his fluid intake. As a result, he required medical intervention for severe dehydration and constipation.

“What Michael needed was for me to be an affirming mental health care provider and to ask him about his lived experience,” Schwindt said. “When I finally did that, then we were able to bring in a team of people and work with Michael. You can’t medicate away discrimination.”

Schwindt also brought up the discouraging suicide rate in the trans community: about 40% attempt suicide. She emphasized the importance of assessing for specific gender-identity conversion efforts, which may contribute to a trans patient’s suicidal ideation.

Overall, Schwindt reminded the conference attendees, “affirmative mental health care requires a holistic, client-centered approach, especially in the case of transgender and gender-diverse patients.”
Exploring the Link Between Migraine and PTSD

Leah Kuntz

Previous studies have found links between migraine and other psychiatric disorders, including bipolar disorder, peripartum depression, and attention-deficit/hyperactivity disorder. Now, research points to a common genetic basis for both migraine and posttraumatic stress disorder (PTSD). The results further suggest shared risk factors, thus partially explaining the comorbidity of these conditions.

“Our results suggest that common genes and signaling pathways are involved in PTSD and migraine, and this might explain why PTSD and migraine can co-occur frequently,” said senior author on the study, Divya Mehta, PhD, of the Queensland University of Technology. “This might further imply that common environmental risk factors for both PTSD and migraine might be acting on these genes.”

The study observed 6 pairs of monozygotic (MZ) twins discordant for PTSD and 15 pairs of MZ twins discordant for migraine. PTSD was assessed via phone interviews conducted by an experienced interviewer using structured questions and DSM-IV criteria. All 6 pairs of twins were identified as having experienced a PTSD-qualifying potentially traumatic event as per the DSM-IV criteria. Migraine was assessed using International Headache Society diagnostic criteria (International Classification of Headache Disorders, Third Edition) together with a diagnosis of migraine with or without aura. Pairs of twins discordant for migraine in the discordant migraine twins to dissect common genes in posttraumatic stress disorder and migraine.

Blood samples were taken from all participants. Association between DNA methylation and PTSD status was tested using linear mixed effects models with age, sex, and cell counts as covariates. Using the same study design as the PTSD sample of twins, the 15 pairs of MZ twins discordant for migraine were tested for association of methylation at genetic loci that overlap between PTSD and migraine using varied analyses.

“At the epigenome-wide level, researchers assessed how many of the 1036 genes associated with PTSD overlapped with those significantly associated with migraine in the discordant migraine twins,” Mehta explained. “We identified DAPK2 and TM6SF2 as two of the top overlapping genes between the two disorders. DAPK2 is a calmodulin-regulated protein kinase; it has been implicated in the intracellular degradation process essential for adaptation to metabolic stress (autophagy). TM6SF2 is associated with cardiovascular disease and plays a role in oxidative stress. These findings suggest that epigenetic changes in response to different types of stress may ‘mediate’ stress phenotypes,” the study authors explained.

“To the best of our knowledge, this is the first study to examine overlapping genes and biological processes in PTSD and migraine comorbidity using the monozygotic co-twin design,” the authors reported. “These results are important and suggest that common genes and pathways might be associated with PTSD and migraine, with implications for diagnosis of comorbidities in PTSD and common treatments for these comorbid disorders.”

“These results may have implications for treatments, as one medicine or therapy might only be effective for a single disorder,” Mehta added. “For co-occurring disorders such as PTSD and migraine, once we know which common genes are implicated in both disorders, we can develop new therapeutics to target these, thereby reducing symptoms and curing both.”

REFERENCES
Psychiatrists’ Response to Human Trafficking

Lujain Alhajji, MD; Maria Hadjikyriakou, MD; and Vanessa Padilla, MD

Human trafficking is a public health issue that involves exploiting individuals for forced sex or labor. Traffickers perpetuate the cycle of exploitation by utilizing methods such as emotional, economic, or physical abuse; isolation; and threats. Physical, mental, legal, and social sequelae of human trafficking can persist for years after individuals survive their trafficking situations. Individuals with a preexisting history of psychiatric illnesses, including substance use disorders, are especially vulnerable to being trafficked.

Human trafficking is a problem worldwide, including in the United States (Figure 1). The practice is not limited to cities; it is also prevalent in suburbs and rural towns. There are misconceptions that victims are only foreign-born individuals, members of minority groups, and/or people who come from low socioeconomic backgrounds. The truth, however, is that victims can be of any race, gender, nationality, socioeconomic group, or background. In addition to sex trafficking, human trafficking also consists of forced labor across both legitimate and illegitimate businesses, including sweatshops, massage parlors, agriculture, and domestic service (eg, cleaning, childcare, elder care), and travel and service industries (Figure 2).

Survivors experience many barriers in accessing health care services; among them are a sense of fear, distrust, shame, guilt, isolation, and worry.

ACTIVITY GOAL
The goal of this activity is to provide psychiatrists with information to better understand, recognize, and address sequelae related to human trafficking.

LEARNING OBJECTIVES
After engaging with the content of this CE activity, you should be better prepared to:

- Recognize risk factors and potential identifiers of human trafficking, including medical and psychiatric sequelae.
- Identify trauma-informed approaches in evaluating human trafficking victims and survivors.

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

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Sexual Abuse
1,184
Physical abuse
1780
Abuse issues 1898
False promises/fraud
438
Posing as a benefactor
Job offer/advertisement
515
Familial
1067
Intimate partner/marriage
366
Unstable housing
368
Recent migration/relocation
2364
Runaway homeless youth
90
Criminal record/criminal history
1866
Excessive working hours
2043
Threat to report to immigration
Verbal abuse
1640
Withholds pay/earnings
279
Withholds/denies needs
1254
Substance use concern
53
Physical health concern
53
Occupational health concern
90
Withholds pay/earnings
1254
Frequent violent incidents
90
Lack of control over personal schedule, money, or identification documents
90
Controlling compassion who insists on providing the history, does not allow for privacy, or insists on translating for patient
90
Living at work or living in overcrowded locations
90
Not allowed to take breaks at work to eat or drink
90
Recently recruited for different work than usual
90

Figure 2.
A Closer Look at Types of Human Trafficking

SEX TRAFFICKING
8248 Situations of sex trafficking
14,597 Individual victims and survivors of sex trafficking

LABOR TRAFFICKING
1236 Situations of labor trafficking
4934 Individual victims and survivors of labor trafficking

SEX AND LABOR TRAFFICKING
505 Situations of sex and labor trafficking
1048 Individual victims and survivors of sex and labor trafficking

TOP 5 RISK FACTORS/VULNERABILITIES FOR TRAFFICKING VICTIMIZATION

SEX TRAFFICKING
Substance use concern
Recent migration/relocation
Runaway homeless youth
Recent migration/relocation
Unstable housing
Mental health concern

LABOR TRAFFICKING
Unstable housing
Crime
record/criminal history
Physical health concern
Substance use concern

TOP 3 IDENTIFIED TYPES
SEX TRAFFICKING
1 Escort services
2 Illicit massage, health, and beauty
3 Pornography

LABOR TRAFFICKING
1 Domestic work
2 Agriculture and animal husbandry
3 Travelling sales crews

TOP 5 RECRUITMENT TACTICS
SEX TRAFFICKING
Intimate partner/marriage
proposition
Familial
Job offer/advertisement
Posing as a benefactor
Faked promises/fraud

LABOR TRAFFICKING
Job offer/advertisement
False promises/fraud
Smuggling-related
Familial
Posing as a benefactor

TOP 5 FORMS OF FORCE, FRAUD, AND COERCION
SEX TRAFFICKING
Induces/exploits substance abuse issues
Physical abuse
Sexual abuse
Intimidation - displays/threatens weapons
Emotional abuse - intimacy related

LABOR TRAFFICKING
Withholds pay/earnings
Excessive working hours
Threat to report to immigration
Verbal abuse
Withholds/denies needs

Table 1. Red Flags That May Indicate Human Trafficking

<table>
<thead>
<tr>
<th>Physical red flags</th>
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<tbody>
<tr>
<td>Untreated/untreated workplace injuries</td>
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<tr>
<td>Signs of physical or sexual abuse, malnourishment</td>
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<tr>
<td>Branding tattoos including “property of…,” “daddy,” or an individual’s name or initials in prominent places</td>
</tr>
<tr>
<td>Exposure to toxic chemicals</td>
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<tr>
<td>Multiple unintended pregnancies/terminations</td>
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<tr>
<td>Frequent sexually transmitted infections and genital injuries</td>
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<tr>
<td>Communicable and noncommunicable diseases (e.g., tuberculosis, hepatitis)</td>
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<tr>
<td>Dental issues</td>
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<table>
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<tr>
<th>Behavioral red flags</th>
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</thead>
<tbody>
<tr>
<td>Inconsistent or scripted history</td>
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<tr>
<td>Submissive, fearful, anxious, evasive, uncooperative, avoidant, or hostile behavior</td>
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<tr>
<td>Unable to provide home address</td>
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<tr>
<td>High number of sexual partners or frequent runaway incidents in minors</td>
</tr>
<tr>
<td>Depression, anxiety, trauma-related, or substance use disorders</td>
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<tr>
<td>Uses language common in commercial sex (e.g., referring to trafficker and associates as daddy/family/boyfriend)</td>
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<table>
<thead>
<tr>
<th>Environmental red flags</th>
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<tr>
<td>Lack of control over personal schedule, money, or identification documents</td>
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<tr>
<td>Controlling compassion who insists on providing the history, does not allow for privacy, or insists on translating for patient</td>
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<td>Living at work or living in overcrowded locations</td>
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<tr>
<td>Not allowed to take breaks at work to eat or drink</td>
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<tr>
<td>Recently recruited for different work than usual</td>
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Assessment
Studies have shown that up to 88% of human trafficking victims had contact with a health care provider while actively being trafficked, which means opportunities were missed to help the victim. This is especially true in emergency departments, family medicine clinics, and obstetrics and gynecology settings. Among the cited barriers to the proper identification and care of human trafficking victims and survivors are the lack of hospital screening protocols for human trafficking; a high volume of patients seen by clinicians with time constraints that keep patient interactions short; and the burden of documentation. In addition, physicians, including psychiatrists, seldom receive the necessary education on human trafficking that would help reduce missed opportunities for identifying victims.

Psychiatrists are leaders in trauma-informed care and experts in the assessment and management of psychiatric disorders. Thus, psychiatrists stand in a unique position to bridge victims and individualized multidisciplinary resources, as well as to provide education on human trafficking to other clinicians, health care providers, trainees, and students. As a result, it is imperative that psychiatrists learn to screen for and identify potential human trafficking victims within the health care system in order to better address victims’ and survivors’ physical and mental health needs.

The goal of screening for human trafficking should not be for the purpose of disclosure—as it can retraumatize a patient who may not be ready to disclose—but rather to assess the need for and inform the patient of available resources.
Table 1 lists potential physical, behavioral, and environmental red flags to look for during an encounter that may alert a psychiatrist to a potential human trafficking victim.12,13

The National Human Trafficking Resource Center provides a suggested protocol flowchart for use in a hospital-wide setting, which includes several questions that can be used in the assessment of human trafficking (Figure 3).14 Further research is needed to develop and validate brief, effective tools for physicians that will help in identifying children, youth, and adults who are being trafficked for sex and/or labor or who are at risk of such exploitation.15

Beyond screening tools, a patient who is trafficked or at risk of being trafficked should feel comfortable sharing their concerns and experiences with physicians. It is thus recommended that physicians utilize the 6 principles of trauma-informed care when evaluating any patient with suspected trafficking experience (Table 2).16 A physician utilizing these principles is able to understand the impact of trauma, recognize the signs and symptoms of traumatic stress, and respond to the patient in a nonjudgmental and respectful manner in order to empower the patient without retraumatization. The PEARR tool (Table 3) can help physicians assess and assist human trafficking victims via a trauma-informed approach.17

CASE VIGNETTE

“Ms. Zankowski,” aged 28 years, is a female patient with a history of migraine headaches and hepatitis C who presented to her primary care physician for her annual physical evaluation. She disclosed a prior diagnosis of posttraumatic stress disorder relating to physical and sexual abuse during childhood, followed by a history of experienced violence as an adult. She also reported a history of alcohol use disorder and cannabis use disorder.

Ms. Zankowski reported fleeing her family home at age 18 years to escape the family abuse. An older man found her on the street and promised her protection, housing, and food. After earning her trust, he began to pimp her, threatening to kill her if she told anyone. Ms. Zankowski spent the next 10 years being forced to sell her body on the streets under the control of a series of traffickers. She coped with this trauma by drinking alcohol and smoking cannabis.

Ms. Zankowski had a prior psychiatric hospitalization for a suicide attempt and was discharged on sertraline 100 mg daily. She was unable to adhere to sertraline on an outpatient basis due to her inability to access her identification cards or health care services while under the control of her trafficker.

After some time, Ms. Zankowski was able to escape her trafficker and reside safely in a women’s shelter. After being assigned a case manager at the shelter, Ms. Zankowski was able to get connected to health care resources including a visit to a primary care physician. By establishing a nonjudgmental, collaborative, and therapeutic doctor-patient relationship, Ms. Zankowski was slowly able to trust her primary care physician enough for her to open up about her posttraumatic stress disorder and prior trauma history. Her primary care physician connected her with preventive care services and referred her to an integrated psychiatry care clinic for survivors of human trafficking. This specialty clinic provided psychiatry, psychology, social work, and case management services.

Ms. Zankowski subsequently was restarted on sertraline and began individual psychotherapy. She started to attend Alcoholics Anonymous meetings and participated in an ongoing relapse prevention plan. She enrolled in vocational services and planned to complete a General Educational Development program. As a result of the trauma-informed care provided, she benefited from peer support services within a safe, trustworthy, and multidisciplinary clinical environment. As she moved forward, Ms. Zankowski felt empowered to make choices for herself and to use her voice to express her feelings.
Table 2. Six Principles That Guide a Trauma-Informed Approach

<table>
<thead>
<tr>
<th>Safety</th>
<th>Trustworthiness and transparency</th>
<th>Peer support</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Collaboration and mutuality</td>
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</table>

Table 3. The PEARR Tool

<table>
<thead>
<tr>
<th>STEP 1: Provide privacy</th>
<th>STEP 2: Educate</th>
<th>STEP 3: Ask</th>
<th>STEP 4: Respect and respond</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provide a patient with a safe and private setting.</td>
<td>Educate the patient about abuse, neglect, and violence in a nonjudgmental and normalized manner.</td>
<td>Screen the patient for abuse, neglect, or violence.</td>
<td>Offer the patient information about resources that can assist in the event of an emergency (eg, local service providers, crisis hotlines). If the patient accepts help, refer to, and provide information for, local and national resources as appropriate.</td>
</tr>
<tr>
<td>Consider strategies to separate the patient from the companion in a nonthreatening manner.</td>
<td>Determine risk factors.</td>
<td>If the adult patient denies victimization or declines assistance, then respect the patient’s wishes.</td>
<td></td>
</tr>
<tr>
<td>Explain any limits to confidentiality (eg, mandatory reporting for minors).</td>
<td>Provide the patient with educational resources/contact info, preferably on a small card or item that the patient can hide in their belongings.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Future Directions

Multidisciplinary teams and integrated psychiatry care are crucial to meeting human trafficking survivors’ health care and psychosocial needs (Table 4). By understanding human trafficking, educating health care providers about trauma and trauma-informed care, developing screening tools, expanding access to care, and promoting partnerships with health care professionals across different disciplines and the community, integrated care models can support survivors and build a stronger response to end human trafficking. Amplifying survivors’ voices and establishing equal partnerships with survivors of human trafficking is essential in enhancing antitrafficking education for health care providers.15

Dr Alhajji is an assistant professor in the Department of Psychiatry and Behavioral Sciences at the University of Miami Miller School of Medicine. Dr Hadjikyriakou is a Consultation-Liaison Psychiatry fellow at the University of Miami Miller School of Medicine. Dr Padilla is Consultation-Liaison Psychiatry Fellowship Program Director at the University of Miami Miller School of Medicine.

References


PERs

Behavioral participants' theoretical and practical knowledge learned in the course. It will conclude with an exam (optional) testing technique, management of complications, post-ECT management, and covered include patient selection and preparation, ECT and anesthesia, as well as a poster session for abstracts. The call for abstracts is now open. Submit your work today!

Save the Dates

31st Annual Meeting
April 23–24, 2022

Traditionally an in-person conference, this year’s event will be held virtually for the second time. It is set to include plenary presentations by leading experts in the fields of ECT, TMS, and other novel brain stimulation therapies, as well as a poster session for abstracts. The call for abstracts is now open. Submit your work today!

ECT Certificate Course
May 14–15, 2022

A virtual course on electroconvulsive therapy (ECT), this event will consist of two half days of didactic and practicum experiences. Topics covered include patient selection and preparation, ECT and anesthesia technique, management of complications, post-ECT management, and medicolegal issues. It will conclude with an exam (optional) testing participants’ theoretical and practical knowledge learned in the course.

We invite you to join our team! The California Department of State Hospitals (DSH) is the largest forensic mental health hospital system in the nation. We’re looking for qualified psychiatrists to work as Medical Directors at our locations in California.

As a Medical Director at a DSH hospital, you will serve as the primary physician leader of the hospital. You’ll have the opportunity to oversee clinical practice, diagnostic and evaluative activities, treatment programs, and care of patients at the facility you’re working at.

DSH offers an outstanding quality of practice; we maintain a number of academic partnerships and promote a team-oriented, collegial working environment. We also offer all our psychiatrists a competitive salary, a world-class benefits package, and excellent work-life balance.

If you’re interested in this exciting opportunity, email your CV to careers@dsh.ca.gov today!
California

**Psychiatrist Needed**

- California Correctional Facilities: $275 - $325 Plus/hr.
- Department of the State Hospitals: $280 - $290/hr.
- LA-DMH & LA County Jail: $300/hour - group rate
- Tulare County Adult Jail: $185 - $265/hr.
- San Diego County Psych Hospital: $260/hr - $270/hr.
- SDCPH Telepsychiatry: $160/evaluation
- Tele-Psychiatry: $180-$220/hr.

New York

**Psychiatrist Needed**

- Psychiatrist: $200 - $350/hr.
- All NYC & Upstate Locations Available

Ref. Bonus/Signing Bonus up to $2k/$2k (*Certain Rules Apply)

A+ Occurrence Malpractice Through PRMS

Imperial Locum has started using Jump Recruiter for its updated job posting.

www.JumpRecruiter.com

Call: 559.799.8344
599.786.5228 / 599.791.0932
Fax: 888.712.2412
Email: imperiallocum@imperiallocum.com
Visit: www.imperiallocum.com

AACAP’s 2022 Virtual Pediatric Psychopharmacology Update Institute

**Working Hands-On With Master Clinicians**

On-Demand Content: January 18 – February 28, 2022
Live Virtual Sessions: January 29 – January 30, 2022

Gabrielle A. Carlson, MD, and James J. McGough, MD, Co-Chairs

AACAP's 2022 Virtual Pediatric Psychopharmacology Update Institute attempts to describe up-to-date, evidence-based pharmacological approaches to managing disorders commonly evaluated and treated by child and adolescent psychiatrists. Ten child and adolescent psychiatrists and clinical researchers discuss implementing clinical practice changes, and attendees participate in Q&A panel discussions as well as case-based small group sessions with these master clinicians.

This meeting will allow you to earn up to 14.5 AMA PRA Category 1 Credits™ right from the comfort of your home or office, and will be comprised of a combination of on-demand and live virtual learning from experts in the field.

Visit www.aacap.org/psychopharm-2022 for more information!

AACAP’s 69th Annual Meeting

October 17-22, 2022 - Toronto, Ontario CANADA

James J. McGough, MD, Program Chair

Submissions to the Call for Papers for AACAP’s 69th Annual Meeting will open in December and will be due February 15, 2022, or June 7, 2022, for (late) New Research Posters.

The Call for Papers submission form will be available at www.aacap.org/AnnualMeeting-2022, and all submissions must be made online. Abstract proposals are prerequisites for acceptance of any presentation. Topics may include any aspect of child and adolescent psychiatry.

RECRUITING FULL TIME & PER DIEM PSYCHIATRISTS
NEW YORK METRO AREAS

Northwell Health’s Behavioral Health Service Line strives to address the diverse mental health needs of the communities we serve by providing a continuum of accessible, high quality psychiatric and substance abuse services including emergency, crisis, inpatient, and outpatient programs for people of all ages. Northwell’s clinical programs are complemented by a robust education, training, and research enterprise, including the world-renowned Psychiatry Research Department at The Zucker Hillside Hospital, which has led cutting-edge investigations that have meaningfully influenced many lives.

TO BOLSTER OUR NETWORK OF OUTSTANDING CARE PROVIDERS,
WE ARE RECRUITING BOARD ELIGIBLE/BORDE CERTIFIED PSYCHIATRISTS FOR THE FOLLOWING POSITIONS:

**ASSOCIATE DIRECTOR, PEDIATRIC EMERGENCY PSYCHIATRY**

Cohen Children’s Medical Center
New Hyde Park, NY

**CHILD AND ADOLESCENT PSYCHIATRIST, SCHOOL MENTAL HEALTH**

Cohen Children’s Medical Center
New Hyde Park, NY

**OUTPATIENT PSYCHIATRIST, PHELPS CONTINUING DAY TREATMENT PROGRAM**

PHELPS Memorial Hospital
Sleepy Hollow, NY

**PHYSICIAN-IN-CHARGE, PERINATAL PSYCHIATRY**

The Zucker Hillside Hospital
Glen Oaks, NY

**ADULT OUTPATIENT PSYCHIATRIST**

The Zucker Hillside Hospital
Glen Oaks, NY

**VICE CHAIR, PSYCHIATRY**

Staten Island University Hospital
Staten Island, NY

**MEDICAL DIRECTOR, LGBTQ TRANSGENDER MEDICINE**

The Zucker Hillside Hospital
Glen Oaks, NY

**FULL-TIME ADDICTION MEDICINE**

Staten Island University Hospital
Staten Island, NY

**EMERGENCY PSYCHIATRIST, PER DIEM**

Long Island Jewish Medical Center
New Hyde Park, NY

**ASSISTANT MEDICAL DIRECTOR, CONSULTATION TELEPSYCHIATRY**

Lenox Health
Greenwich Village, NY

Per Diem and Moonlighting positions available at most locations

Benefits at Northwell Health include:

- Nationally competitive salaries
- Comprehensive benefits package
- Four weeks’ vacation plus paid conference/CME time
- Academic appointment commensurate with experience
- Advanced education opportunities
- College Tuition reimbursement for dependent children

Qualified candidates should forward their CV to Alice Perkins: OPR@Northwell.edu

Our Geriatric Psychiatry Fellowship is now accepting applications.
We are seeking full-time, board-certified psychiatrist applicants with outstanding clinical and managerial skills who have a passion for leading, directing and developing an academically-oriented behavioral health center of excellence. The Vice Chairperson will provide senior oversight of hospital-based services at Staten Island University Hospital. The Vice Chair will work collaboratively with hospital and health system leaders to meet and exceed the departments organizational, clinical, operational, and financial goals.

Responsibilities include clinician recruitment, education, supervision, strategic development, and process improvement initiatives.

**Required Education and Experience**

- M.D. or D.O. Degree, or equivalent, from an accredited institution (ACGME or foreign program that is similarly accredited)
- Completion of a Residency in Psychiatry with Board Certification.
- Minimum of three (3) years of clinical practice in psychiatric medicine and previous leadership experience
- Must be licensed as a physician in the State of New York
- Experience in a leadership role in a hospital department, preferably in a major medical center or health system, required.

For more information and to apply, qualified candidates should forward their CV to Alice Perkins, OPR@Northwell.edu

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**PSYCHIATRISTS**

**PSYCHIATRIC INPATIENT PROGRAM**

- **$280,344 – $336,864**
  - Annual salary (Board Certified)
- **$273,156 – $327,360**
  - Annual salary (Board Eligible)

---

**The Behavioral Service Line at Northwell Health is recruiting for a**

**Vice Chairperson,**

**Staten Island University Hospital**

We are seeking full-time, board-certified psychiatrist applicants with outstanding clinical and managerial skills who have a passion for leading, directing and developing an academically-oriented behavioral health center of excellence. The Vice Chairperson will provide senior oversight of hospital-based services at Staten Island University Hospital. The Vice Chair will work collaboratively with hospital and health system leaders to meet and exceed the departments organizational, clinical, operational, and financial goals. Responsibilities include clinician recruitment, education, supervision, strategic development, and process improvement initiatives.

**Required Education and Experience**

- M.D. or D.O. Degree, or equivalent, from an accredited institution (ACGME or foreign program that is similarly accredited)
- Completion of a Residency in Psychiatry with Board Certification.
- Minimum of three (3) years of clinical practice in psychiatric medicine and previous leadership experience
- Must be licensed as a physician in the State of New York
- Experience in a leadership role in a hospital department, preferably in a major medical center or health system, required.

For more information and to apply, qualified candidates should forward their CV to Alice Perkins, OPR@Northwell.edu

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**No disability evaluations. No benzodiazepines. No stimulants. No insurance companies.**

- 40-hour workweek with flexible schedules, including 4/10s
- Thank You Bonus up to $20k for professionals newly hired with the State of CA
- Generous paid time off and holiday schedule
- Multiple locations throughout CA
- 401(k) and 457 plans (tax defer up to $39k–$52k per year)
- Paid malpractice insurance, license, and DEA renewal
- Relocation assistance available to professionals newly hired with the State of CA
- Visa sponsorship opportunities
- State of CA retirement that vests in five years (visit www.CalPERS.ca.gov for retirement formulas)

---

**EOS**

**YOU BELONG HERE.**

Submit your CV to CentralizedHiringUnit@cdcr.ca.gov; or apply online at www.cchcs.ca.gov.

Salary depending on experience. In addition to a CA medical license, you must possess documentation of COVID-19 vaccination or medical/religious exemption.
Outpatient Psychiatry Opportunity
San Joaquin County Behavioral Health Services is seeking to fill Outpatient Adult [General], and Sub-Speciality Psychiatry (Child Psychiatry, Geriatric, Forensic, Addiction and Psychosomatic Medicine) positions in a multidisciplinary, recovery-oriented clinical setting. Services are provided either on-site or using a hybrid model of on-site and tele-psychiatry practice. The positions offer a very competitive salary with a guaranteed base, plus incentive opportunities, board certified Psychiatrists have the potential to earn over $300K+ annually.

Interested J-1 and H-1B candidates are welcome to apply.
Fax your CV to 209-468-2399 or email to BHSadministration@sjcbhs.org. EOE

Full-time psychiatrist for a large public health & hospital system in the Silicon Valley
-$275,080-$357,600 annually in 36 days of annual leave Full benefits & relocation
(Above annual salary includes additional pay for Board Certification and Acute Settings)

Santa Clara Valley Health and Hospital System, a public healthcare system in the heart of Silicon Valley, is seeking full-time BE/BC psychiatrists for a variety of clinical settings, including emergency psychiatric services, inpatient consultation liaison services, jail custody health inpatient services, specialty mental health outpatient services and primary care behavioral health services.

As the largest public health care system in northern California, we offer comprehensive healthcare resources to a large and diverse patient population. Psychiatrists are part of a robust team of staff that work in collaboration with other medical specialties and behavioral health clinicians to provide integrated health care to patients.

Psychiatrists are eligible for numerous benefits including 36 days of annual leave, 5 days of educational leave, 12 holidays, $45000 educational funds, health benefits, life insurance and CalPERS retirement plan. Call no required.

In addition, part-time opportunities for BE/BC psychiatrists, PGY IIIs and IVs are available.

If you are interested in working in a dynamic and collegial work environment, please submit a CV and letter of interest to MD.Recruitment@hhs.sccgov.org. EOE

Join the team at Ocean View Adult Psychiatric Hospital! Conveniently located just off the 405 freeway in Long Beach, CA, we are just a short distance to major cities in both Los Angeles County and Orange County. Ocean View is a voluntary psychiatric unit that provides the highest quality care to patients 18 years of age or older with Medicare or private insurance. Consisting of mostly single occupancy rooms, we offer a private and comfortable inpatient setting that promotes healing.

We are seeking board-certified physicians, nurse practitioners, and physician assistants to join our team of providers. Interested candidates, please e-mail your confidential CV to: Jessica Rodriguez at 661-368-0826

We’re committed to making Better Health easier. Looking for an amazing place to live, work and play?
We’re actively recruiting physicians specializing in psychiatry to join our dynamic and growing multi-specialty physician group with opportunities throughout New York City! Comprised of over 4000 physicians and healthcare professionals, our culturally diverse and world-class teams provide services to NYC Health + Hospitals (HHH), the largest public health system in the United States.

Become part of our North Bronx Healthcare Network, affiliated with Albert Einstein College of Medicine, and located in attractive and safe residential Bronx neighborhoods, just 20 minutes from Manhattan. Our facilities offer a full continuum of acute care inpatient and outpatient services within diverse Medical and Surgical specialties, including Psychiatry. Along with employing evidence-based best practices in providing the highest level of quality care to our patients, we utilize a patient-centered approach that is respectful of their individuality, culture, and community.

New York City Health + Hospitals/Jacobi
The Department of Psychiatry offers 89 Adult, Acute Inpatient beds, a Comprehensive Psychiatric Emergency Program (CPEP), a Consultation-Liaison Service, Adult Ambulatory Practice, Intensive Outpatient Program, and a Community-Based Assertive Community Treatment Program. Openings available include:

- Attending Psychiatrist - Inpatient Psychiatry Service
- Attending Psychiatrist - CPEP
- Attending Child Psychiatrist - CPEP

We offer a generous compensation package, along with unparalleled health benefits, opportunities for advancement, retirement plan, malpractice, Sponsorship for H1 J Visa, and much more! For immediate consideration, please contact Joe Mastov – Physician Recruiter, at: Mastov@pagny.org, call 646-895-3875, or apply online at: www.pagny.org

New York City Health + Hospitals/North Central Bronx
The Department of Psychiatry has 70 Adult and Geriatric Acute Inpatient Beds, a Partial Hospital Program, Psychiatric Emergency Service, Consultation-Liaison Service, an Adult Ambulatory Practice, and a Community-Based Assertive Community Treatment Program. Openings available include:

- Director of Psychiatry - Emergency Services
- Attending Psychiatric Emergency Service
- Attending Psychiatric Services
- Attending Psychiatric Services - CPEP
- Attending Psychiatric Services - CPEP
- Attending Child Psychiatrist - CPEP

We are an Equal Opportunity Employer M/F/D/V

https://www.youtube.com/watch?v=KcOj44OCU88=6s
We are an Equal Opportunity Employer M/F/D/V
Missouri

Compass Health

Psychiatrist

Provide full-time face-to-face psychiatric services to patients in Raymore, MO for a minimum of 40 hours a week. In addition, may provide services to patients in Royal Oaks Hospital in Windsor, Missouri, as assigned. M.D. or professional equivalent degree, BC/BE in Psychiatry and Missouri medical license required. This position is eligible for the Employee Referral Program. Position is with Compass Health, Inc., dba Pathways Community Health in Clinton, MO. Send C.V. to: Ms. Cathy Grigg, Director of Psychiatry Services at cgrigg@phbc.org. Fax: 417-532-6606.

North Carolina

Cape Fear Valley

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:

Emergency Opportunity

Two BE/BC providers with experience in ED or trained in ED/Psychiatry. The Emergency Department maintains a Psychiatric Unit of 9 beds for patients in crisis. Support team is specialty trained. Schedule consists of 16 hour shifts, approximately 10 shifts per month.

Adult Outpatient Opportunity

BE/BC provider with training/experience in a variety of mental health treatment conditions as well as Chemical Dependency and Substance Abuse. Candidate with experience in treatment of Bipolar Disorder, Borderline Personality Disorder, and Mood Disorders is preferred. Additionally, ECT training and experience is highly desirable. Well established adult team is flexible and transparent for either or both inpatient and outpatient services. Clinic hours are Monday - Friday with limited call.

Child Outpatient Opportunity

BE/BC Child Psychiatrist. Current structure is for 90% outpatient Monday through Friday work schedule.

We offer best in class compensation plus generous benefits including Paid Malpractice, CME Time and Continuing Education. Further, the Department is keenly interested in diversifying its faculty and staff and encourages applications from diverse candidates. Candidates from historically under-represented group(s) in higher education and medicine are encouraged to apply. Candidates who possess personal characteristics that might be considered as diversifying elements among the clinical team and the larger psychiatry faculty at UMMS are invited to identify themselves during the application process.

Telecare Corporation

Telecare is looking for patient centered providers to join our rapidly growing Physician Services Organization. Following locations have immediate openings:

- Regional Medical Director, Northern CA. Schedule: 30 hours per week. Leadership Opportunity! Alameda, CA
- Partners in Wellness Schedule: 24 hours per week. San Jose, CA
- El Dorado PHF Schedule: 40 hours per week. Placerville, CA
- La Claridad, CA Schedule: 40 hours per week. San Jose, CA
- Heritage PHF Schedule: 40 hours per week. Leadership Opportunity! Oakland, CA
- Sacramento FACT Schedule: 20 hours per week. Forensic experience a plus! Sacramento, CA
- Alameda AOT Schedule: 24 hours per week. Oakland, CA
- Regional DDMI Programs Schedule: 40 hours per week. Flexible schedule! Northern CA
- TAO Central Schedule: 16 hours per week. Orange, CA
- For additional listings, please visit: www.telecarecorp.com/physician-jobs/

You will work as part of a multidisciplinary team. The staff is all very friendly, and it is a supportive working environment.

Please email your resume to Psorecruiting@telecarecorp.com

EOE M/F/V/Disability
Ohio

VitalCare Health Strategies, is looking for a part-time Psychiatrist for our facility at Warren County Jail in Lebanon, Ohio. The schedule is 4 hours per week and the days are negotiable. Clinical care can be given through telepsych or a combination of telepsych and on-site coverage. This position would serve as the collaborating Physician. There will also be coverage through a Psychiatric APRN.

Please contact Morgan Garrett MGarrett@VitalCareHS.com

Oregon

Opportunity to practice in Oregon!

This full-time position offers teaching and patient care in an outpatient setting. You will be providing patient care 80% of the time and spend the remaining time supervising residents or participating in academic duties.

Job Requirements
- Board Certified or Board Eligible in Psychiatry
- Current Oregon Licensure or eligibility
- Knowledge of working with patients who have chronic health conditions
- Experience in psychodynamic psychotherapy preferred

Benefits include:
- Competitive compensation
- Medical malpractice paid
- Continuing medical education
- Relocation allowance
- Starting bonus

For more information, or to apply please visit www.samhealth.org/DocJobs or contact Valerie Fulleton at 541-768-4766.

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:

- Carrier Clinic - Staff Psychiatrist (Belle Mead, NJ)
- Consultation Liaison Psychiatrists: Raritan Bay Medical Center (Perth Amboy)
- Medical Director ED/Crisis: Jersey Shore University Medical Center (Neptune, NJ)
- Inpatient: Raritan Bay Medical Center (Perth Amboy, NJ)
- Outpatient: Ocean Medical Center (Red Bank, NJ)
- Medical Director for Adult Inpatient Unit: Riverview Medical Center (Red Bank, NJ)
- Outpatient: Southern Ocean Medical Center (Manahawkin, NJ)
- Outpatient Child & Adolescent Psychiatrist: Hackensack University Medical Center (Hackensack, NJ)
- Geriatric Psychiatry: Hackensack University Medical Center (Hackensack, NJ)
- Telehealth Remote Psychiatrist FT/PT

Renee.Theobald@hmhn.org or call: 908 - 839 - 5693
**Brief Summary:** For full prescribing information and patient information, refer to package insert.

**INDICATION AND USAGE**

INGREZZA (val benzine) capsules is indicated for the treatment of adults with tardive dyskinesia.

**CONTRAINDICATIONS**

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

**WARNINGS AND PRECAUTIONS**

**Somnolence**

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

**QT Prolongation**

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

**Parkinsonism**

INGREZZA may cause parkinsonism in patients with tardive dyskinesia. Parkinsonism has also been observed 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:

- Hyperesthesia
- 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 645 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 treatment with antipsychotic therapy. Event types were reported in a manner that preserved confidentiality for the individual patient.

**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 Greater than Placebo**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>INGREZZA (n=293) (%)</th>
<th>Placebo (n=153) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence (somnolence, fatigue, sedation)</td>
<td>10.0%</td>
<td>4.3%</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Akathisia (akathisia, restlessness)</td>
<td>2.7%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>2.3%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Musculoskeletal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2.3%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

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

**Other Adverse Reactions Observed During the 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 uninformative, 4) which were not considered to have clinically significant implications, or 5) which occurred at a rate equal to or less than placebo.

Other Adverse Reactions Observed During the Premarketing Evaluation of INGREZZA

- Other Adverse Reactions Observed During the Premarketing Evaluation of INGREZZA

**DRUG INTERACTIONS**

**Diseases Having Clinically Important Interactions with INGREZZA**

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

**Monoamine Oxidase Inhibitors (MAOIs)**

Clinical Implication: 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.

Prevention or Management: Avoid concomitant use of INGREZZA with MAOIs.

Examples: Isocarboxazid, phenelzine, selegiline

**Strong CYP3A4 Inhibitors**

Clinical Implication: Concomitant use of INGREZZA with strong CYP3A4 inhibitors increased the exposure (Cmax and AUC) to valbenazine’s 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.

Prevention or Management: Reduce INGREZZA dose when INGREZZA is coadministered with a strong CYP3A4 inhibitor.

Examples: Itraconazole, ketoconazole, clarithromycin

**Strong CYP2D6 Inhibitors**

Clinical Implication: Concomitant use of INGREZZA with strong CYP2D6 inhibitions 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.

Prevention or Management: Reduce INGREZZA dose when INGREZZA is coadministered with a strong CYP2D6 inhibitor.

Examples: Paroxetine, fluoxetine, quinidine

**Strong CYP3A4 Inducers**

Clinical Implication: 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.

Prevention or Management: Concomitant use of strong CYP3A4 inducers with INGREZZA is not recommended.

Examples: Rifampin, carbamazepine, phenytoin, St. John’s wort

**Digoxin**

Clinical Implication: Concomitant use of INGREZZA with digoxin increased digoxin levels because of inhibition of intestinal P-glycoprotein (P-gp).

Prevention or Management: 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.

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

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

**OVERDOSAGE**

**Human Experience**

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

**Management of Overdose**

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

For further information on INGREZZA, call 84 INGREZZA (844-647-3902).

**Distributed by:**

Neurocrine Biosciences, Inc.
San Diego, CA 92130

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THE SIMPLE CHOICE
FOR YOUR ADULT PATIENTS
WITH TARDIVE DYSKINESIA (TD)

Only INGREZZA offers all the ease of:

- One capsule, once daily
- Effective dosing options
- No titration required
- Taken any time of day
- Taken with or without food

Give your patients all the ease of INGREZZA. See more at INGREZZAHCP.com/Dosing

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 (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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RE: REL-1017 Major Depressive Disorder (MDD)

Dear Doctor,

The clinical research department in our practice is now enrolling into the Phase 3 RELIANCE Clinical Research Program with Relmada Therapeutics. The program will evaluate the therapeutic efficacy and safety of REL-1017 for participants with major depressive disorder (MDD) in placebo-controlled studies as an adjunctive (add-on) treatment with an antidepressant therapy or as a monotherapy treatment (if not currently taking an antidepressant). Eligible participants in any study who complete the 28 days of treatment will be offered to continue into the open label extension study in which all participants will receive the investigation medication for up to 1 year. The open label study is also open to participants who did not first participate in a placebo-controlled study.

Basic inclusion criteria include:

- Age 18-65
- MDD diagnosis by SCID-5 and currently experiencing a major depressive episode
- BMI between 18 and 30 at screening, BMI up to 35 for open label

There is a screening process involving the patient to determine eligibility. All study related visits and tests are covered by the Sponsor. I look forward to speaking with potential patients in your practice who may be interested in participating. Please do not hesitate to contact me with any questions or concerns. You may also have your patients contact our research team directly at medical@relmada.com. Thank you for your time and attention in considering appropriate referrals as we all understand your support contributes to advancing treatment options.

Sincerely,
Marc de Somer MD, MBA, ScD, MPH, MSc