When the welcome news of effective vaccines for COVID-19 arrived in December 2020, the country shared a collective sigh of relief. Yet, the hard work was still in front of us. One fact always remains true in medicine: We have limited resources (ie, manpower, medications, hospital beds, organs, etc) with which to treat the population. In this instance, the overriding question was how would we, as a society, determine who gets the first shots?

Three primary ethical frameworks have guided COVID-19 vaccine allocation and prioritization in the United States. According to the Centers for Disease Control (CDC), methamphetamine use resurged in the United States from 2015 to 2018, rising to an annual use rate of 59.7 per 1000 adults, or 14,686,900 individuals per year.¹

The continued escalation of methamphetamine use, alone or with opioids, presents providers with complex medical challenges and difficult consequences for patients, families, and the legal and health care systems. Separately, each drug represents an epidemic and a crisis. Together, they magnify the medical complications facing our society.

Continued on Page 10

Commentary

What About Us? The Marginalization of Serious Mental Health and Substance Use

The fairest rules are those to which everyone would agree if they did not know how much power they would have. – John Rawls

Michael W. Jann, PharmD

Continued on Page 12

Issue Highlights

Psychiatric Communities
Helping LGBTQ Youth During the Pandemic
Stewart Adelson, MD, Joanne Ahola, MD, Mary Barber, MD, Flavio Casoy, MD, Jack Drescher, MD, and Laura Erickson-Schroth, MD

Mood Disorders
Lithium Dosing for Optimal Renal Safety
David N. Osser, MD

Addiction & Substance Use
What Can Be Done About the Methamphetamine Epidemic?
Michael W. Jann, PharmD

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PsychiatricTimes.com
#1 PRESCRIBED ONCE-MONTHLY LONG-ACTING INJECTABLE ATYPICAL ANTIPSYCHOTIC

INVEGA SUSTENNA®

FOR THE TREATMENT OF SCHIZOPHRENIA IN ADULTS

DON’T WAIT UNTIL THERE’S NOTHING LEFT TO LOSE

Missing doses of oral antipsychotics can cause repeated relapse. With each relapse comes the risk of losing the progress that you have made together.

See the safety and efficacy results of a study where INVEGA SUSTENNA® significantly delayed time to relapse vs commonly prescribed oral antipsychotics.

To view the data, simply scan this QR code or visit InvegaSustennaHCP.com

Consider transitioning appropriate adult patients to INVEGA SUSTENNA®

*The study was not powered to compare the efficacy of INVEGA SUSTENNA® with that of individual oral antipsychotics.

INDICATION

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

- Schizophrenia 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.

Actor Portrayal
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 fatal strokes, have been 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 and rhabdomyolysis and 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 QTc prolongation such as the occurrence of torsades de pointes 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 ketoacidosis, 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., dehydration, 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, fracture of or other 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 levels, and the elevation persists during chronic administration. Paliperidone has a prolactin-elevating effect similar to risperidone, which is 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 CYP3A4/5–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 dosing 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 extra pyramidal and/or withdrawal symptoms in neonates with third trimester exposure. Advise patients to notify their healthcare professional if they become pregnant or intend to become pregnant during treatment with INVEGA SUSTENNA®. Patients should be advised that there is a 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 (≥5% twice placebo) were injection site reactions, somnolence/sedation, dizziness, akathisia and extra pyramidal disorder.

Please see the Brief Summary of the full Prescribing Information, including Boxed WARNING, for INVEGA SUSTENNA® on the following pages.

cp-64200v3

REFERENCES:

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In a long-term open-label pharmacovigilance and safety study in subjects with schizophrenia in which the highest dose available (234 mg) was evaluated, INVEGA SUSTENNA® was associated with a mean change in glucose of +1.4% or mg/dL. During the initial 25-week open-label period of a long-term study in subjects with schizoaffective disorder, INVEGA SUSTENNA® was associated with a mean change in glucose of +5.3% (±158). At the endpoint of the subsequent 15-month double-blind period of the study, INVEGA SUSTENNA® was associated with a mean change in glucose of +8.3% (±141) compared with a mean change of -0.0% in the placebo group (±26).}

**Dyslipidemia**

Unfavorable alterations in lipids have been observed in patients treated with atypical antipsychotics.

**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 presence of NMS and its associated hyperthermia.**

**Hyperosmolar coma or death, have been reported in patients treated with all atypical antipsychotics.**

**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 ketoacidosis or hyperosmolar coma or death, have been reported in patients treated with all atypical antipsychotics. These cases were the most part, seen in post-marketing clinical trials and epidemiologic studies, not in clinic trials. Hyperglycemia and diabetes have been reported in trial subjects treated with INVEGA SUSTENNA®. 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 clear. However, epidemiological studies suggest an increased risk of hyperglycemia-related adverse reactions in patients treated with the atypical antipsychotics.

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

<table>
<thead>
<tr>
<th>Group</th>
<th>Change from baseline</th>
<th>Mean change from baseline (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-1.3</td>
<td>0.1</td>
</tr>
<tr>
<td>INVEGA SUSTENNA®</td>
<td>1.2</td>
<td>-1.8</td>
</tr>
</tbody>
</table>

**Table 2: Change in Fasting Lipids from Four-Place-Controlled, 9- to 13-Week, Fixed-Dose Studies in Subjects with Schizophrenia**

<table>
<thead>
<tr>
<th>Group</th>
<th>Cholesterol</th>
<th>Triglycerides</th>
<th>LDL</th>
<th>HDL</th>
<th>Change from baseline</th>
<th>Mean change from baseline (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>2.0%</td>
<td>-2.1%</td>
<td>11.9%</td>
<td>1.3%</td>
<td>9.8%</td>
<td>0%</td>
</tr>
<tr>
<td>INVEGA SUSTENNA®</td>
<td>2.1%</td>
<td>-1.0%</td>
<td>-2.4%</td>
<td>0%</td>
<td>11.0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

**Table 3: Proportion of Patients with Changes in Fasting Lipids**

<table>
<thead>
<tr>
<th>Group</th>
<th>Proportion of Patients with Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>20.0%</td>
</tr>
<tr>
<td>INVEGA SUSTENNA®</td>
<td>21.9%</td>
</tr>
</tbody>
</table>

**Table 4: Mean Changes in Serum Glucose**

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean change from baseline (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-1.0</td>
</tr>
<tr>
<td>INVEGA SUSTENNA®</td>
<td>1.8</td>
</tr>
</tbody>
</table>

**Table 5: Mean Changes in Serum Triglycerides**

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean change from baseline (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-0.9</td>
</tr>
<tr>
<td>INVEGA SUSTENNA®</td>
<td>9.4</td>
</tr>
</tbody>
</table>

**W 

**Hyponatremia**

Hyponatremia has been reported in patients treated with atypical antipsychotics, including paliperidone and INVEGA SUSTENNA®.

**Hyperkalemia and Dihydropyridine-Related Adverse Reactions**

**Table 6: Change in Mean Serum Cholesterol, Triglycerides, HDL, and LDL Levels**

<table>
<thead>
<tr>
<th>Group</th>
<th>Serum Cholesterol</th>
<th>Serum Triglycerides</th>
<th>Serum HDL</th>
<th>Serum LDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>2.0%</td>
<td>-2.1%</td>
<td>11.9%</td>
<td>1.3%</td>
</tr>
<tr>
<td>INVEGA SUSTENNA®</td>
<td>2.1%</td>
<td>-1.0%</td>
<td>-2.4%</td>
<td>0%</td>
</tr>
</tbody>
</table>

**Table 7: Proportion of Patients with Changes in Mean Serum Cholesterol, Triglycerides, HDL, and LDL Levels**

<table>
<thead>
<tr>
<th>Group</th>
<th>Proportion of Patients with Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>20.0%</td>
</tr>
<tr>
<td>INVEGA SUSTENNA®</td>
<td>21.9%</td>
</tr>
</tbody>
</table>

**Table 8: Mean Changes in Serum Glucose**

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean change from baseline (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-1.0</td>
</tr>
<tr>
<td>INVEGA SUSTENNA®</td>
<td>1.8</td>
</tr>
</tbody>
</table>

**Table 9: Mean Changes in Serum Triglycerides**

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean change from baseline (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-0.9</td>
</tr>
<tr>
<td>INVEGA SUSTENNA®</td>
<td>9.4</td>
</tr>
</tbody>
</table>
In a long-term open-label pharmacokinetic and safety study in subjects with schizophrenia in which the highest dose achieved (234 mg) was achieved by 13% of subjects, mean changes from baseline in lipids values are presented in Table 5.

Table 5: Change in Fasting Lipids from an Open-Label and Double-Blind Periods of a Long-Term Study in Subjects with Schizophrenia

<table>
<thead>
<tr>
<th>Open-Label Period</th>
<th>Double-Blind Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>INVEGA SUSTENNA®</td>
<td>Placebo</td>
</tr>
<tr>
<td>Mean change from baseline (mg/dL)</td>
<td>Mean change from baseline (mg/dL)</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>LDL</td>
</tr>
<tr>
<td>n=451</td>
<td>n=116</td>
</tr>
<tr>
<td>n=161</td>
<td>n=162</td>
</tr>
<tr>
<td>-0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>3.3%</td>
<td>6.0%</td>
</tr>
</tbody>
</table>

Weight Gain

Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended. Data on mean changes in body weight and the proportion of subjects meeting a weight gain criterion of ≥7% of body weight from the four placebo-controlled (control 9 weeks and double-blind 13 weeks) fixed-dose studies in subjects with schizophrenia are presented in Table 5.

Table 5: Mean Change in Body Weight (kg) and the Proportion of Subjects with ≥7% Weight Gain from Baseline

<table>
<thead>
<tr>
<th>Placebo</th>
<th>INVEGA SUSTENNA®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>n=451</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>0.4</td>
</tr>
<tr>
<td>Weight Gain ≥ 7% increase from baseline</td>
<td>3.3%</td>
</tr>
</tbody>
</table>

Orthostatic Hypotension and Syncope

Paliperidone can induce orthostatic hypotension and syncope in some patients because of its alpha-adrenergic blocking activity. Syncope was reported in <1% (4/2792) of subjects treated with INVEGA SUSTENNA® in the recommended dose range of 39 mg to 234 mg in the four fixed-dose, double-blind, placebo-controlled trials compared with 0% (0/110) of subjects treated in the placebo group. In the four fixed-dose efficacy studies in subjects with schizophrenia, orthostatic hypotension was reported as an adverse event by <1% (2/2129) of INVEGA SUSTENNA®-treated subjects compared to 0% (0/159) in placebo. Incidences of orthostatic hypotension and syncope in the long-term studies in subjects with schizophrenia and schizophrenia disorder is similar to those observed in the short-term studies. INVEGA SUSTENNA® should be used with caution in patients with known cardiovascular disease (e.g., heart failure, history of myocardial infarction or ischemia, conduction abnormalities), cerebrovascular disease, or conditions that predispose the patient to hypotension (e.g., dehydratation, hypotension, and treatment with antihypertensive medications). Monitoring of orthostatic vital signs should be considered in patients who are vulnerable to hypotension.

Falls

Somnolence, postural hypotension, motor and sensory instability have been reported with the use of atypical 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 temporally related to antipsychotic agents, including INVEGA SUSTENNA®, agranulocytosis has also been reported. The mean changes from baseline in lipids values during the initial 25-week open-label period and at the endpoint of the subsequent 15-month double-blind period in a long-term study in schizophrenia subjects are described in Table 7.

Table 7: Change in Fasting Lipids from an Open-Label and Double-Blind Periods of a Long-Term Study in Subjects with Schizophrenia

<table>
<thead>
<tr>
<th>INVEGA SUSTENNA® (paliperidone palmitate)</th>
<th>extended-release injectable suspension, for intramuscular use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monitor patients with clinically significant neutropenia for fewer or other symptoms or signs of infection and neutropenic sepsis. Indeed, neutropenic sepsis is a rare adverse event with INVEGA SUSTENNA® in patients with severe neutropenia (absolute neutrophil count &lt;1000/mm³) and follow their WBC until recovery.</td>
<td></td>
</tr>
</tbody>
</table>

Hyperprolactinemia

Like other drugs that antagonize dopamine D2 receptors, paliperidone elevates prolactin levels and the elevation persists during chronic administration. Paliperidone has a prolactin-elevating effect similar to that seen with reserpine, a drug that is associated with anoestrus and anovulation.

Hyperprolactinemia, 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 pre-clinical and male rodents. Galactorrhea and gynecomastia have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinaemia when associated with hypogonadism may lead to decreased bone density in both male and female subjects. Tissue culture experiments indicate that approximately 50% 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 previous breast cancer. An increase in size of any pre-existing galactorrhea or breast lumps, and a higher proportion of females experienced potentially prolactin-related adverse reactions compared to males (5.8% vs. 0.3%). Amenorrhea (2.5%) in females and no single potentially prolactin-related adverse reaction in males was observed with a rate greater than 2%.

Schizophrenia

INVEGA SUSTENNA® in patients with schizoaffective disorder (Study SCA-3004) see Clinical Studies (14.2); elevations of prolactin to the above reference range (>18 ng/mL in males and >30 ng/mL in females) relative to open-label baseline at any time during the double-blind phase were noted in 16.2% of males treated with the INVEGA SUSTENNA® group than those in the placebo group in males (55.6% vs. 22.3%) and in females (44.4% vs. 25.6%). During the 15-month double-blind period of the phase 3 INVEGA SUSTENNA® group had 14 potentially related to hyperprolactinemia, and a higher proportion of females experienced potentially prolactin-related adverse reactions compared to males (5.8% vs. 0.3%). Amenorrhea (2.5%) in females and no single potentially prolactin-related adverse reaction in males was observed with a rate greater than 2%.

Somnolence, sedation, and dizziness were reported as adverse reactions in subjects treated with INVEGA SUSTENNA® (see Adverse Reactions). Antipsychotics, including INVEGA SUSTENNA®, have the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that paliperidone therapy does not adversely affect them.

Seizures

In the four fixed-dose double-blind placebo-controlled studies in subjects with schizophrenia, <1% (1/1283) of patients treated with INVEGA SUSTENNA® in the recommended dose range of 39 mg to 234 mg experienced an adverse event of convulsion compared with <1% (1/110) of placebo-treated subjects who experienced an adverse event of grand mal convulsion.

Like other antipsychotic drugs, INVEGA SUSTENNA® should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in patients 65 years or older.

Discontinuation of Body Temperature Regulation

Protection of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Paliperidone may have potential to impair judgment, thinking, or motor skills. Patients should be cautioned about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that paliperidone therapy does not adversely affect them.

Seizures

In the four fixed-dose double-blind placebo-controlled studies in subjects with schizophrenia, <1% (1/1283) of patients treated with INVEGA SUSTENNA® in the recommended dose range of 39 mg to 234 mg experienced an adverse event of convulsion compared with <1% (1/110) of placebo-treated subjects who experienced an adverse event of grand mal convulsion.

Like other antipsychotic drugs, INVEGA SUSTENNA® should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in patients 65 years or older.

Discontinuation of Body Temperature Regulation

Paliperidone may have potential to impair judgment, thinking, or motor skills. Patients should be cautioned about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that paliperidone therapy does not adversely affect them.
Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described in this section are derived from a clinical trial database consisting of a total of 3817 subjects (approximately 1707 patient-years exposure) with schizophrenia who received at least one dose of INVEGA SUSTENNA® in the recommended dose range of 39 mg to 234 mg and a total of 510 subjects with schizophrenia who received placebo. Among the 3817 INVEGA SUSTENNA®-treated subjects, 1280 received INVEGA SUSTENNA® in four fixed-dose, double-blind, placebo-controlled trials (one 9-week and three 13-week studies). 849 received INVEGA SUSTENNA® in the maintenance trials (median exposure 229 days during the initial 33-week open-label phase of this study, of which 205 continued to receive INVEGA SUSTENNA® during the double-blind, placebo-controlled phase of this study [median exposure 171 days]), and 1675 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 [debridal-glacial] cross-over trial). One of the 13-week studies included 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® (paliperidone palmitate) in adult subjects with schizophrenia. A total of 236 subjects received INVEGA SUSTENNA® during the 15-month, open-label period of this study; 218 subjects received schizophrenia treatment with a combination of psychotherapies. 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 681 subjects received INVEGA SUSTENNA® during the initial 25-week open-label period of this study (median exposure 147 days); 146 subjects continued to receive INVEGA SUSTENNA® during the 15-month double-blind placebo-controlled period of this study (median exposure 446 days). Adverse reactions that occurred more frequently among INVEGA SUSTENNA®-treated group (a 2% difference or more between groups) were: weight increased, nasopharyngitis, headache, hyperprolactinemia, and pyrexia.

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

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 9.3% 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 trials in subjects with schizophrenia, who 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.

Adverse Reactions Occurring at an Incidence of 2% or More in INVEGA SUSTENNA®-Treated Patients:

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>Placebo®</th>
<th>Placebo® (N=302)</th>
<th>Placebo® (N=312)</th>
<th>INVEGA SUSTENNA® (N=163)</th>
<th>INVEGA SUSTENNA® (N=165)</th>
<th>INVEGA SUSTENNA® (N=223)</th>
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</thead>
<tbody>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Back pain</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Musculoskeletal stiffness</td>
<td>1 &lt;1 1 &lt;1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
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<td>1</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Pain in extremity</td>
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<td></td>
<td></td>
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<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Akathisia</td>
<td>3 2 3 1 5 6 7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extrapyramidal disorder</td>
<td>5 5 5 3 3 0 0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence/sedation</td>
<td>3 5 7 4 1 5 5</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
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<tr>
<td>Psychiatric disorders</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Agitation</td>
<td>7 10 5 9 8 5 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>7 8 5 3 6 6 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>Nightime</td>
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<td></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>
</tr>
<tr>
<td>Cough</td>
<td>3 3 1 0 1 1 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1 2 1 1 1 1 0</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

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

a Placebo group is pooled from all studies and included either delirium or global injection depending on study design.

b Initial deltid injection of 234 mg followed by either 38 mg, 156 mg, or 234 mg every 4 weeks by deltid or global injection.

c Other dose groups (39 mg, 78 mg, and 156 mg) are from studies involving only global injection. (see Clinical Studies (14.1) in Full Prescribing Information).

d 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 disorder, abdominal pain/upper stomach discomfort, and tachycardia/sinus tachycardia/heart rate increased. All injection site reaction-related adverse reactions were collapsed and are grouped under “Injection site reactions.”

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) for which a drug cause was not assigned 3) which were so general as to be uninformative, or 4) which were not considered to have significant clinical implications.

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

Eur and labyrinth disorders: vertigo

Eye disorders: eye movement disorder, eye rolling, oculargic crisis, vision blurred

Gastrointestinal disorders: constipation, dyspepsia, flatulence, saliva hypersecretion

Immun system disorders: hypersensitivity

Investigations: alanine aminotransferase increased, aspartate aminotransferase increased, electrocardiogram abnormal

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

Musculoskeletal and connective tissue disorders: arthralgia, joint stiffness, muscle rigidity, muscle spasms, muscle tightness, muscle twitching, skeletal rigidity

Nervous system disorders: bradykinesia, cerebrovascular accident, cogwheel rigidity, convulsion, dizziness, postural, slurring, dysarthria, dyskinesia, dystonia, hypotonia, lathyrism, uninformal dystonia, parkinsonism, psychomotor hyperactivity, syncope

Psychiatric disorders: insomnia, libido decreased, restlessness

Reproductive system and breast disorders: amenorrhea, breast, 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 generalized, 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-Abacus global scale which broadly evaluates parkinsonism, (2) the Barnes Akathisia Rating Scale global clinical rating score which evaluates akathisia, and (4) use of anticholinergic medications to treat EPS (Table 3), and (5) incidence of spontaneous reports of EPS (Table 8).

Table 7: Extrapyramidal Symptoms (EPS) Assessed by Incidence of Rating Scales and Use of Anticholinergic Medication - Schizophrenia Studies in Adults

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>INVEGA SUSTENNA®</th>
<th>Placebo®</th>
<th>Placebo® (N=163)</th>
<th>INVEGA SUSTENNA® (N=130)</th>
<th>INVEGA SUSTENNA® (N=156)</th>
<th>INVEGA SUSTENNA® (N=228)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parkinsum®</td>
<td>0 9 12 10 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Akathisia®</td>
<td>5 2 3 1 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyskenia®</td>
<td>3 4 6 6 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of Anticholinergic Medications</td>
<td>12 10 12 11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For parkinsonism®, percent of subjects with Simpson-Abacus Total score ≥ 0.3 at endpoint (Total score defined as total sum of items score divided by the number of items).

For akathisia®, percent of subjects with Barnes Akathisia Rating Scale global clinical rating score which evaluates akathisia.

For dyskenia®, percent of subjects with a score ≥ 3 on any of the first 7 items or a score ≥ 2 on two or more of any of the first 7 items of the Abnormal Voluntary Movement Scale at endpoint.

Percent of subjects who received anticholinergic medications to treat EPS.
Additional Adverse Reactions Reported in Clinical Trials with Oral Paliperidone 

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

Cardiac disorders: bundle branch block left, sinus arrhythmia 

Gastrointestinal disorders: abdominal pain, small intestinal obstruction 

General disorders and administration site conditions: edema, edema peripheral 

Immune system disorders: anaphylactic reaction 

Infections and infestations: rhinitis 

Musculoskeletal and connective tissue disorders: musculoskeletal pain, torticollis, trismus 

Nervous system disorders: grand mal convulsion, parkinsonian gait, transient ischemic attack 

Psychiatric disorders: sleep disorder 

Reproductive system and breast disorders: breast engorgement 

Respiratory, thoracic and mediastinal disorders: pharyngolaryngeal pain, pneumonia aspiration 

Skin and subcutaneous tissue disorders: rash palmar 

Vascular disorders: hypertension, ischemia 

Postmarketing Experience 

The following adverse reactions have been identified during postapproval use of paliperidone; because these reactions were reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: angiospasm, catatonia, ileus, somnolence, swelling tongue, thrombotic thrombocytopenia purpura, uterine incontinence, and uterine retention. 

Cases of anaphylactic reaction after injection with INVEGA SUSTENNA® have been reported during postmarketing surveillance from studies with oral paliperidone palmitate. 

Paliperidone is the major active metabolite of risperidone. Adverse reactions reported with oral risperidone and paliperidone palmitate may include: anaphylactic reaction, edema, edema peripheral. 

Drug Interactions 

Drug-Drug Interactions with INVEGA SUSTENNA®: 

Drugs Having Clinically Important Interactions with INVEGA SUSTENNA®: 

Because paliperidone palmitate is hydrolyzed to paliperidone (see Clinical Pharmacology (12.3) in Full Prescribing Information), drug interactions with oral products that have this potential (see Adverse Reactions) may occur when INVEGA SUSTENNA® is co-administered with another CNS-active agent. 

Drug interactions may occur if INVEGA SUSTENNA® is co-administered with other CNS-active drugs, alcohol, or other CNS-active agents that have this potential (see Adverse Reactions). 

INVEGA SUSTENNA® should be used with caution in combination with other centrally acting drugs and alcohol (see Adverse Reactions). 

INVEGA SUSTENNA® should be used with caution in combination with other centrally acting drugs and alcohol (see Adverse Reactions).
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 injectable suspension during the period of organogenesis at doses up to 250 mg/kg, which is 10 times MRHD of 224 mg paliperidone based on mg/m² body surface area.

In animal reproduction studies, there were no increases in fetal anomalies when pregnant rats and rabbits were treated orally with paliperidone during the period of organogenesis with up to 8 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. Cleft palate was observed in the offspring of pregnant mice treated with risperidone at 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 6 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 0.8 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 0.5 to 1.2 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 mg² body surface area; it is not known whether these deaths were due to a direct effect of the fetuses or pups or to effects on the dams (see RISPERIDAN® 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 in breastfed infants exposed to paliperidone’s parent compound, risperidone.

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).

Females and Males of Reproductive Potential
Infertility
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 in 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 similar to those in children and adolescents receiving the MRHD of risperidone. In addition, a delay in sexual maturation was seen at all doses in both males and females. The above effects showed little or no reversibility in females after a 12-week drug-free recovery period.

The long-term effects of INVEGA SUSTENNA® on growth and sexual maturation have not been fully evaluated in children and 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 (2.5) 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 50 mL/min to < 80 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 Dementia with Lewy Bodies can experience increased sensitivity to INVEGA SUSTENNA®. Manifestations can include confusion, obtundation, postural instability with frequent falls, extrapyramidal symptoms, and clinical features consistent with neuroleptic malignant syndrome.

DRUG ABUSE AND DEPENDENCE
Controlled Substance
INVEGA SUSTENNA® (paliperidone) 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.
Tackling the Big Issues

As this issue went to press, the Centers for Disease Control and Prevention reported that about 50% of the US adult population had received at least 1 dose of the COVID-19 vaccine. Despite new variants and continued behavioral challenges worldwide, the progress made in addressing the pandemic is enormous, reminding us that we can—and should—do better in other areas of medicine, health care, and societal issues. Such is the case with the methamphetamine epidemic. While the opioid epidemic raged through the country and caught the attention of doctors, lawmakers, and others, the methamphetamine epidemic lurked in the shadows. This problem received less consideration even though, as Michael W. Jann, PharmD, discusses in the lead article, the 2 drugs are often used concurrently. Great strides have been made toward understanding and addressing the opioid epidemic; hopefully, in the future, we will report the same for methamphetamine.

Meanwhile, Cynthia M. A. Geppert, MD, MA, MPH, MSBE, DPS, MSJ, reflects on the progress of the COVID-19 vaccine distribution but asks, “What about us?” In her commentary, Geppert ponders parity and whether patients with serious mental illness and substance use disorders (as well as the psychiatrists caring for them) were properly prioritized in the receipt of the vaccines. In doing so, she renews the call for advocacy for patients with mental illness to improve care now and in the future.

This issue also features a Special Report on sexual and gender minority youth, a population facing increased challenges and at risk of mental health issues. With thanks to Special Report Chair Jack Turban, MD, this collection of articles shines a light on a population for whom the health care system can do better. As Turban explains, psychiatrists are in a unique position to foster positive affirmations for youth, both as a part of clinical care and as educators in the community.

As usual, this issue of Psychiatric Times™ features clinical pieces with practical guidance for supporting the patients in your care. This month’s Research Update looks at the pharmacotherapies that are most effective for schizophrenia. Meanwhile, 2 articles explore the impact of psychiatric illness on the whole patient and provide suggestions to protect their well-being. David N. Osser, MD, explores lithium dosing in renal patients, while Kawna K. Haldeman, MD, reviews the impact of psychosomatic medicine to improve care now and in the future.

As we have learned from our tango with COVID-19, there is no challenge we cannot overcome when we work together to find and implement solutions. Our country and the field of psychiatry continue to face these and other difficult issues. Yet, with continued dedication on behalf of all of you, we are sure to realize more successes and positive outcomes in the days, months, and years to come!
FROM THE EDITOR

Aiding and Abetting Burnout

John J. Miller, MD | Editor in Chief

I often think back with fondness about clinical psychiatric practice in the early 1990s, a time when I could meet with patients for an hour weekly when indicated, and prescribing was as simple as choosing the medication I felt was most appropriate for the patient sitting in front of me. I feel sad for psychiatrists who completed their residencies after the year 2000 and have only known the burdensome bureaucratic protocols that currently dictate our options for the treatment of our patients.

There are many old dirt roads I could drive you down related to this topic, but I will limit this editorial to 3:

1. The Medicare “drug formulary”
2. The loss of medication coverage when our patient changes health plans
3. The imposition of step therapy requirements by insurance companies

In clinical medicine, case reports have always provided the best vehicle for teaching, so I will share my experiences with patients over the past 5 years to exemplify these policies. These experiences are only examples of larger problems and trends, which regrettably contribute to physician burnout. The medication-related elements of these cases are factual; however, I have changed patient names and other identifying details to ensure privacy.

Part D. Although Tom remained psychiatrically stable, he was eventually approved for disability.

From Maximus Federal Services was:

*“Geodon (ziprasidone) is requested for ongoing treatment of major depression and obsessive-compulsive symptoms, which are off-label (non-FDA approved).”*
did not have a diagnosis for the FDA-approved in-
lowed him to maintain full time employment. How-
the clozapine, Steve experienced sedation as a sig-
Significantly, he has maintained the same full-time
symptom of his schizophrenia, and he has learned
auditory hallucinations, he understands them as a
stable for the past 5 years, fully adherent with treat-
4 times a day (with a 12-hour post dose serum
ago aggressive treatment with 4 different antipsychotic
no symptom improvement over the next year with
time he was floridly psychotic with constant audi-
a diagnosis of schizophrenia 7 years prior, at which
had several denials of coverage of medications
from Medicare, involving stable patients who were
doing quite well on a chronic medication regimen
but then, because they aged into their Medicare
benefits, they lost coverage for their chronic but
stable medication because it was not FDA ap-
proved for the prescribed diagnosis.

Patient Changed Health Plan, Chronic Coverage Denied
“Steve” is a 29-year-old single man who received a
diagnosis of schizophrenia 7 years prior, at which
time he was floridly psychotic with constant audi-
dary hallucinations and paranoid delusions. After
no symptom improvement over the next year with
gressive treatment with 4 different antipsychotic
medications, he was hospitalized and treated with
clozapine. Upon discharge, I gradually increased
the clozapine dose, because of a lack of response,
to his final maintenance dose of 800 mg by mouth
4 times a day (with a 12-hour post dose serum clozapine
level = 500 ng/mL). Over the following year, he significantly improved and has remained
stable for the past 5 years, fully adherent with treat-
ment. Although he continues with minimal daily
auditory hallucinations, he understands them as a
symptom of his schizophrenia, and he has learned
to push them into the background and ignore them.
Significantly, he has maintained the same full-time
job for the past 4 years and lives independently
with full functionality.

Early during the course of increased titration of
the clozapine, Steve experienced sedation as a sig-
nificant side effect. Ultimately, we began a trial of
modafinil 200 mg by mouth daily, which signifi-
cantly improved his daytime sedation and has al-
lowed him to maintain full time employment. How-
ever, my first prescription for the modafinil was
denied by his private health care plan because Steve
did not have a diagnosis for the FDA-approved in-
dications for modafinil of obstructive sleep apnea,
narcolepsy, or shift work sleep disorder.

After my prior authorization was denied, I called
the health plan and requested a direct review
with their pharmacist, which occurred 10 minutes
later. The pharmacist agreed with my treatment
plan of using the modafinil to manage the sedation
from the clozapine. It was smooth sailing for the
next 5 years; I simply filled out a 1-page prior au-
thorization annually, which was always approved.

Two months ago, Steve’s employer changed to a
new health care plan, and the modafinil refill was
denied coverage because of its off-label use. I have
filled out 2 prior authorizations so far, and both
have been denied. I requested a peer-to-peer re-
view, but the plan denied this, stating they required
a detailed written prior authorization request after
the 2 initial denials before my appeal could be ele-
vated to a peer-to-peer review. I am awaiting the
plan’s response to my written appeal, and Steve is
paying full price for the modafinil.

Step 1, 2, 3 . . . Then Maybe We Will Approve That Drug

“Susan” is a 34-year-old married mother of 2, who
has struggled with recurrent episodes of unipolar
major depression beginning in her early 20s. She
initially responded to psychotherapy and healthy
lifestyle changes, but by her mid-20s her depres-
sion had worsened, and we initiated antidepressant
medication with good effect. Despite medication
compliance over time, her depressive episodes re-
curred and she was treated with courses of 4 differ-
ent antidepressants from different classes over a
2-year period with only partial response.

After discussing treatment options, and for
many clinical reasons, Susan and I agreed to aug-
ment her fluoxetine with brexpiprazole 1mg orally
every day. I provided her samples for the first
month, and she had a good response. When she
went to fill her first prescription at her pharmacy, it
was denied coverage. Susan’s insurance company
would only cover the brexpiprazole after documen-
tation that she had failed trials of 2 other medica-
tions, which they listed as their required policy of
so-called step therapy.

I could have lied, continuing to provide brexpip-
razole samples, while telling Susan’s insurance
company she was failing trials of the 2 required
step therapy treatments, and eventually meet this
insurance company’s step treatment failure. They
would then allow coverage of the drug to which she
responded. However, this is contrary to good med-
ical practice, ethical behavior, and my general phi-
losophy on life. Additionally, it would leave erro-
neous documentation in Susan’s medical record
stating she failed trials of 2 step medications she
never was really prescribed. I called the insurance
company’s appeals department, was graciously
transferred to one of the plan’s reviewing pharma-
cists, explained my clinical treatment plan, and the
brexpiprazole was approved—a rare happy ending, albeit
at the cost of lots of my time.

Discussion
As I move toward the sunset of my career in clini-
cal psychiatry, it saddens me to see how insurance
companies—private, state, federal, Medicaid, Medicare, employer funded—have consistently
obstructed physicians’ decision-making and treat-
ment planning at every opportunity. It is exhaust-
ing, and it certainly contributes to physician burn-
out. Additionally, there is clear socioeconomic dis-
tribution, as these policies are less expensive.
Federal- and state-funded plans impose larger bar-
ers to the treatment plans that the physician has
determined to be best for their patient.

One of my primary frustrations with this pro-
cess is exemplified by Tom and Steve’s stories: If
we limit our prescribing to FDA-approved indica-
tions for medications, we will be in conflict with
our oath to “do no harm” to our patients. The DSM
diagnoses used for clinical trials’ inclusion criteria
to demonstrate efficacy for FDA approval are actu-
ally mythological constructs in constant flux—al-
though they do serve a useful purpose in creating
a common language and approach to treating psychi-
atriotic disorders. An important paper highlighting
this reality concluded that “only 11.8% of DSM-IV-TR diagnoses have an FDA-approved drug.”
When DSM-5 was published in 2013, this percent-
age likely further decreased.

Ultimately, as experts in the field of psychiatry,
we are being strong-armed by bureaucracies that
use fictitious justifications to deny the implemen-
tation of our well-thought-through treatment plans
for our patients. I have discussed this issue in detail
in a previous editorial. Additionally, a good clini-
cian is skilled at identifying patterns of symptoms
that consistently improve when using an FDA-ap-
proved medication for an unrelated diagnosis. The
pervasive obstructionism of insurance payers, based
on ignorant and unethical justifications, further
serves to undermine the quality of care that we at-
tempt to provide to our patients.

With regards to Susan’s story of mandated step
therapy by her insurer, although I was ultimately
able to bypass the 2 required step medications, that
process took a significant amount of time. In the
United States, the intrusion of mandated step ther-
apies has created quite a hardship for physicians in
all specialties. A recent article nicely explored the
current status of this insurance practice, and how
slowly states are passing laws that attempt to push
back on this intrusion.

Conclusion
Every day, medical literature articles appear docu-
menting the contribution of the COVID-19 pan-
demic to physician burnout. Although this phe-
nomenon is significant and pervasive, it is only one
of many daily stressors conspiring to increase our
burnout and the increasing incidence of retiring
early from medical practice. I have reviewed 3 pre-
scribing obstructions imposed intentionally by
insurance payers that contribute to my own burnout;
this has become more significant with each passing
year. The difference is that COVID-19 is not will-
fully and consciously adding to my burnout, whereas the insurance companies are.

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History and Epidemiology
Unlike opioids, methamphetamine lacks US Food and Drug Administration (FDA)-approved pharmacological treatment interventions. Nevertheless, amphetamine-type stimulants (ATS), including methamphetamine, have a unique history that began during World War II; they were then used in the 1950s and 1960s for depression and psychosis.1 ATS use declined in the 1970s after its reclassification to a more restrictive schedule by the Comprehensive Drug Abuse Prevention and Control Act.

Legal restrictions led to new drug forms, and the number of individuals who used methamphetamine grew. Postamphetamine rescheduling led to manufacturing methamphetamine using phenyl-2-propane (P2P) and methylamine. When P2P became a schedule II controlled substance, the number of individuals who used methamphetamine grew. Postamphetamine rescheduling led to manufacturing methamphetamine using phenyl-2-propane (P2P) and methylamine. When P2P became a schedule II controlled substance, ephedrine and pseudoephedrine became the predominant agents used for methamphetamine synthesis. The Combat Methamphetamine Epidemic Act of 2005 limited pseudoephedrine access and banned ephedrine, but these regulations resulted in only a temporary decline in use. In 2005, there were 192,000 new methamphetamine users per year, whereas by 2012, the number had markedly increased to 440,000 individuals per year.2

According to the CDC’s report, methamphetamine use was higher in men compared with women (8.7 vs. 4.7 per 1000 adults, respectively).3 Adults aged 26 to 34 years had the highest rates of methamphetamine use (11.0 per 1000 adults), followed by those aged 18 to 25 years and 35 to 49 years (9.9 and 8.3 per 1000 adults, respectively). The prevalence of methamphetamine use was greater for those making either less than $20,000 per year or between $20,000 and $49,999 per year (15.6 and 7.6 per 1000 adults, respectively), compared with those at other income levels. For almost 45% of those who used the drug, duration of use was greater than 100 days per year; nearly 25% of all individuals who used methamphetamine reported administering the drug intravenously. About 53% met the DSM-5 criteria for methamphetamine use disorder and only 31.5% received substance abuse treatment.

The CDC also compared 2008 hospital admissions with 2017 admissions, finding 15,747,334 drug-related treatment admissions in individuals 12 years or older in 2017.3 The number of treatment admissions due to methamphetamine increased substantially (Figure 1).

These increases in use and treatment translate into a huge economic burden. Using 2005 data, the RAND Corporation estimated total economic costs of $23.4 billion, including indirect costs of about $12.6 billion.2 Based upon increasing usage in the past decade, undoubtedly the economic burden of the drug has substantially increased.

The Twin Epidemics
The opioid epidemic in the United States has been well documented for a decade. The CDC reported that 70,630 fatalities was associated with drug overdoses in 2019, including all drugs.4 That year, the second-highest number of fatalities were associated with stimulant drugs, largely methamphetamine.5 The CDC also compared 2008 hospital admissions with 2017 admissions, finding 15,747,334 drug-related treatment admissions in individuals 12 years or older in 2017.3 The number of treatment admissions due to methamphetamine increased substantially (Figure 2).

Based upon the methamphetamine use and fatality data, it is apparent that it has become a second epidemic and crisis.6 To complicate matters, an increasing number of individuals abuse both opioids and methamphetamine.7 The CDC reported that between 2015 and 2018, 57% of those who used methamphetamine also abused either heroin or prescription opioids.5 Similarly, hospital admissions among individuals who primarily used heroin (but also reported methamphetamine use) increased by 490% from 2008 to 2017.6

The most common administration routes were by (intravenous) IV injection (47.1%) and smoking (46.0%).7 A survey in rural Oregon reported that 96% of participants (N = 112) who used opioids in the past 30 days also noted methamphetamine use, and 50% injected both opioids and methamphetamine.8 Participants indicated that methamphetamine was more widely available, less expensive, and less stigmatized compared with opioids. Individuals discharged from substance abuse programs perceived methamphetamine as a drug that prevented opioid overdose. Individuals who used both opioids and methamphetamine reported that the latter could serve as an opioid substitute, provide a synergistic high, and balance out the sedation from the opioids.8 On the other hand, individuals who used methamphetamine stated that opioids can be used to mitigate the former’s negative adverse effects. They believed that the addition of small amounts of methamphetamine could prolong opioid intoxication effects, and conjugation of both had a more desirable intoxication effect than using either substance alone.8

Pharmacology
Methamphetamine exists in 2 stereoisomer forms, the D- and L-forms; the D-form is 3 to 5 times more potent than the L-form (Figure 3).9 Methamphetamine affects the dopamine, serotonin, and noradrenaline transporters, as well as the vesicular monoamine transporter-2.10 Heroin and other opioids are opioid receptor agonists.11 The opioid receptors are widely distributed in the central nervous system, including the nucleus accumbens (NAcc) and ventral tegmental area (VTA).2 Both methamphetamine and opioids promote the release of dopamine in the NAcc and VTA, indicating a common pharmacological pathway for both drugs regarding reward and reinforcement properties.12 When these agents are taken together, a pharmacodynamic synergy can occur in which dopamine release may be greater than with either agent taken alone. Further, stimulant actions may attenuate an opioid’s sedative actions, whereas opioids can prevent overstimulation by methamphetamine.

PHARMACOKINETICS. The route of methamphetamine administration affects its pharmacokinetics (Table).10 For instance, the IV route produces the most rapid onset of effects, whereas smoking promotes a slightly slower onset (about 20 minutes). The elimination half-life of methamphetamine is...
between 9 and 12 hours. Its metabolism, shown in Figure 3, is converted to 2 main metabolites: amphetamine (AMP) and the 4-hydroxy (OH) metabolite methamphetamine by the cytochrome P450 (CYP) 2D6 enzyme. The CYP2D6 system is prone to many possible drug-drug interactions and genetic polymorphisms (eg, extensive and poor metabolizers). Although CYP2D6 genotyping has not been conducted in methamphetamine pharmacokinetic studies, in one study, a single participant was reported to have an extremely low formation of AMP and 4-OH methamphetamine compared with the other 11 participants; it was suggested that this individual could be a poor metabolizer of CYP2D6.

ADVERSE EFFECTS. A wide range of adverse effects (eg, psychological issues, withdrawal, overdose, cardiac and other medical problems) is associated with methamphetamine use. The most common psychological effects are agitation, psychosis, and suicidal ideation. Acute methamphetamine-induced psychosis is indistinguishable from acute paranoid schizophrenia with hallucinations and delusions. Hallucinations can be auditory, visual, and tactile, with delusions of persecution and reference. Psychosis can occur with doses greater than 50 mg, with an onset ranging from 7 minutes to 3 hours post drug administration. Fatalities from severe psychological effects include those related to accidents, suicides, and homicides. Withdrawal symptoms include insomnia, depressed mood/anxiety, cravings, reduced energy, and cognitive impairment. Agitation, dilated pupils, hypertension, tachycardia, and rapid respiration occur in overdose situations. The cardiac effects can include arrhythmias, hypertension, and sudden death. Other medical problems include pulmonary damage from smoking, pulmonary hypertension, rhabdomyolysis, cerebrovascular strokes, and seizures.

NEUROTOXICITY AND BRAIN INJURY. Unlike other drugs of abuse, methamphetamine has been shown to cause significant neurotoxicity and possible brain injury by modulating at least 3 molecular cascades that involve oxidative stress, neurotoxicity, and excitotoxic effects, and neuroinflammation. Briefly, it alters sigma-1 receptors that increase reactive oxygen and peroxide formation, which leads to oxidative stress. Methamphetamine promotes glutamate transmission, increasing Ca2+ intracellular concentration, resulting in neurotoxic and excitotoxic effects. The third mechanism involves the drug binding to toll-like receptor 4 and activating proinflammatory cytokines (eg, interleukin-6) leading to neuroinflammation. It has been suggested that chronic methamphetamine exposure prior to a traumatic brain injury (TBI) can magnify the injury and worsens outcomes. Conversely, individuals with a TBI seem to be more vulnerable to the neurotoxic effects of methamphetamine use.

Drug Use Chemsex
Part of the recent increase in methamphetamine use may be associated with drug use and sex. Drug use before and during sex is known as chemsex, and methamphetamine is the most commonly abused drug for chemsex among men who have sex with men (MSM). It is frequently used along with gamma-hydroxybutyric acid to enhance the sexual experience. In one study, it was reported that of MSM aged 36 to 44 years, 36% had had chemsex with multiple partners. Some reported having chemsex with more than 10 partners during 1 session. The same study reported that methamphetamine use is typically associated with unprotected sex. MSM who participated in chemsex reported use more than 2 times per month with experiences taking place over the course of years. HIV, other sexually transmitted infections, and other medical complications become major concerns for individuals who engage in chemsex.

The COVID-19 Pandemic
Individuals with substance use problems have been especially affected by COVID-19, and those who use methamphetamine are no exception. The drug can cause pulmonary damage, pulmonary hypertension, and cardiomyopathy, and it compromises pulmonary function, which may make patients more prone to chronic respiratory disease and may put them at risk for more severe illness from COVID-19. Methamphetamine can also impact the immune system by decreasing the efficiency of B cells, macrophages, and other defense mechanisms, further increasing the risk of severity from COVID-19. Risks for and from COVID-19 are even higher for individuals who have HIV and use methamphetamine, because individuals with HIV already have a compromised immune system.

Besides the pulmonary and cardiac damage it causes, methamphetamine use can cause vulnerability to COVID-19 in an additional way: It can further impair an individual’s judgment when used in chemsex by affecting their decision-making regarding pre-exposure prophylaxis or postexposure prophylaxis HIV treatment. This, in turn, enhances vulnerability to contracting COVID-19 and may lead to faster COVID-19 progression.

Treatment
Treatment for drug addictions requires behavioral and, when appropriate, pharmacological interventions. The various behavioral interventions used in individuals with addictions include cognitive behavioral therapy, matrix model, contingency management, motivational enhancement therapy, acceptance and commitment therapy, and 12-step facilitation therapy. Each of these behavioral interventions can be effective in reducing methamphetamine use, but the patient must remain in a given treatment program for the best chance of success.

Although the FDA has made recommendations for medications to counteract opioid abuse, it has not yet done so for methamphetamine abuse. Although many different medications have been tested in randomized clinical trials, only 4 agents—methylphenidate, bupropion, modafinil, and naltrexone—displayed any benefits, and those were limited. None demonstrated adequate and consistent evidence for efficacy. Preliminary pilot studies with small numbers of participants looked at oral naltrexone 150 mg/day, bupropion 300 mg/day, and buprenorphine 8 mg/day; modest reductions were reported in all participants’ methamphetamine withdrawal cravings. Ultimately, some of these agents may have specific uses for addiction interventions.

Bupropion 300 mg/day was reported to be effective in individuals who were methamphetamine-dependent but were low/average users (ie, less than daily). Topiramate 200 mg/day was unable to promote abstinence in those who used methamphetamine but did reduce the amount taken as well as relapse rates in those who were already abstinent. Mir-tazapine 30 mg/day, when used in conjunction with substance use counseling, was associated with decreases in risky sexual activity.

A comprehensive pharmacologic review article on methamphetamine and amphetamine dependence yielded an absence of proven efficacy, although the studies were underpowered with low treatment completion rates.

Combination therapy may be more effective than individual agents. A large multicenter, double-blind, placebo-controlled, randomized clinical trial in individuals with methamphetamine use disorder (N = 403) evaluated the combination treatment of bupropion 450 mg/day and long-acting injection naltrexone 380 mg every 3 weeks. The study was powered at 90% (N = 370 needed) to detect a 24% difference between the combination treatment and the placebo. Two study stages were designed,
each 6 weeks long. Stage 1 assigned participants to the bupropion and naltrazone group (n = 109) or placebo (n = 294) for the first 6 weeks. Participants did not receive a placebo re-choice response was randomly assigned the bupropion and naltrazone and placebo (1:1 ratio) for a second 6-week time period. Urine samples were obtained and tested twice weekly, and the primary outcome was defined as at least 3 methamphetamine-negative samples out of 4 samples at the end of stage 1 or 2. The primary outcome response rate averaged for the 2 stages was 13.6% for the bupropion and naltrazone group and 2.5% for the placebo group, indicating an overall treatment effect of 11.1% (P < .0001). This clinical trial, unlike previous studies, did not lack statistical power and had adequate treatment completions. However, the bupropion and naltrazone response rate was rather low, albeit greater than with the placebo, and illustrates the enormous challenge in finding an effective treatment approach for methamphetamine use disorder.

Concluding Thoughts
Methamphetamine use has been under-recognized compared with the opioid use epidemic, but it is a major health care concern, due to rapidly increasing usage of this drug and its highly addictive pharmacologic properties. Methamphetamine use poses many psycho- logical and physiologic challenges to users. Although behavioral interventions can be effective, there are no FDA-approved drugs for treating methamphetamine addiction.

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opined that the adverse social determinants of health for the SMI population are so entrenched and significant that, ethically, they should constitute a distinct category of health care disparity. If such a designation were formally recognized, it would obviously require vaccine and other potential therapeutic allocation frameworks to rethink the prioritization of SMI.17

In the past, thought leaders as diverse as Pope John Paul II and President Harry Truman stated, in essence, that “a society will be judged on how it treats its weakest members.” Prioritizing COVID-19 vaccination for individuals with SMI and SUDs, people who have long borne a stigma in American health care, promotes the “equal concern” principle of the National Academies. This principle encompasses the idea that every individual has intrinsic worth, dignity, and value, and such prioritization would answer the CDC’s call to remove unfair and avoidable barriers to vaccination as a matter of justice. Even when the scenario is viewed from a classic public health ethics perspective—as De Hert has persuasively argued—protecting the health of the public requires reducing exposure among those cohorts with high probability of exposing others, and among those least likely to take steps to prevent transmission of the virus.18

Given these formidable scientific and ethical arguments for the vaccination of those with SMI and SUD, their comparative neglect in major allocation frameworks likely reflects long-standing systemic social determinants of mental health treatment. These determinants have resulted from lack of economic parity, intrinsic social stigmatization, cultural bias, absence of legal representation, and political disenfranchisement, among many other complex and unjust causes.19

Vaccination Obstacles

The ethical impetus to ensure COVID-19 vaccinations for individuals with SMI and SUD becomes even more urgent when the external and internal obstacles to vaccination among this population are considered. These obstacles are far more formidable than those facing other cohorts who are ranked higher in vaccine allocation protocols. There is a disturbing dearth of research on routine preventive vaccination in the SMI and SUD population, although it is known that the cohort has very low rates of routine vaccination relative to the general population. More encouraging, results of a recent pilot quality improvement project, involving a collaboration with the local public health department, increased preventive vaccination rates in a community outpatient mental health clinic.20 Recent articles offer recommendations for overcoming systems- and individual-level barriers to COVID-19 vaccination for individuals with SMI and SUD, respectively (Table 2).11,21

Individuals with SMI and SUD lacked parity in health care before the pandemic, and COVID-19 has massively exacerbated existing inequalities. These individuals often do not have access to the primary means of health care delivery and of arranging vaccine appointments in the pandemic: electronic communication technology. Patients with SMI often lack the knowledge, skill, and infrastructure to utilize it when it is available. Internal obstacles only compound these external barriers. These include mistrust of the health care system (due to past histories of abuses), low health literacy about COVID-19, and lack of information about the vaccine. A recent set of interviews with individuals with SUDs assessed vaccine readiness and identified significant mistrust among respondents.22 In 2020, the Addiction Policy Forum interviewed 87 individuals about their readiness to receive the COVID-19 vaccine; all were either using substances, in treatment for substance use, or recovering from substance use disorders. Just 45% said they were ready immediately; of the rest, 8% said they would be ready after a delay, 23% were uncertain, and 25% were unwilling to take the vaccine. The reasons participants offered to explain their hesitancy included concerns about the rapid development of the vaccine, potential adverse effects, potential interactions with current medical problems, doubt that they were at serious risk for developing COVID-19, and mistrust of the government.

Mental Health Professionals

Not only patients with psychiatric disorders but also the practitioners who treat them have reason to fear being in the back of the vaccination queue. Health care workers are in phase 1a of the CDC guidance, high-risk health workers are in phase 1a of the National Academies of Science allocation protocol, and Johns Hopkins includes in tier 1 those most essential to sustaining the ongoing COVID-19 response. While most readers of Psychiatric Times23 would likely assume that psychiatrists and other mental health practitioners would be included in all of these phases/tiers, this assumption was not widely shared outside of circles of mental health professionals.

In December, right after the United States Food and Drug Administration’s emergency use authorization of the Pfizer vaccine, Forbes reported that mental health workers feared they would be left out of vaccine protocols.24 This is because state governments exercise considerable independence in how closely they follow national recommendations for allocation. Public health officials and those in the media may not appreciate that, from the beginning of the pandemic to this day, psychiatrists and other mental health professionals have been on the front lines of intensive care units and emergency departments treating patients, often doing so without adequate personal protective equipment.25 Many other mental health practitioners were repeatedly exposed to high-risk patients whose disorders made them unable or unwilling to follow infection-control practices or to take advantage of telehealth options, necessitating in-person visits at community outpatient clinics, inpatient psychiatric units, residential care facilities, and substance use treatment programs.25

In response to this neglect of the mental health workforce in vaccine allocation schemas, the National Association of State Mental Health Program Directors, the National Council of Behavioral Health, and the National Mental Health Corporations of America wrote to Robert R. Redfield Jr, MD, then the CDC director, prior to the Advisory Committee on Immunization Practices issuance of its allocation framework. The mental health organizations argued that mental health practitioners “should be categorized as frontline providers, therefore making them eligible to receive COVID-19 vaccine in its earliest phase of distribution.”26 In May 2020, Elinore McCance-Katz, MD, PhD, who at the time was assistant secretary for Mental Health and Substance Use, had already asserted “that the services provided in mental and substance use disorder treatment programs across the country are essential medical services.”26

Allocation Advocacy Aid

The American Psychiatric Association (APA) has joined these organizations in calling upon its members to actively promote equity in COVID-19 vaccine allocation, issuing a guidance document on the role of the psychiatrist.27 The document affirms that “psychiatrists are uniquely positioned to address many of the public health challenges” that prevent the ideal of equitable vaccine distribution from becoming a reality. The APA lays out practical advice to help psychiatrists educate and counsel their patients about vaccination, including information on how to locate and obtain vaccination in various states.

Psychiatrists know better than almost anyone that an efficacious vaccination campaign directed toward patients with SUD and SMI is necessary but not sufficient to ensure shots in arms. What is most crucial to overcoming vaccine hesitancy and encouraging motivation in these populations is to build on the strength of the therapeutic alliance. Patients trust the recommendation of their psychiatrists or other mental health professionals about vaccination.11,21 There is a compelling obligation for mental health professionals to talk to their patients at every possible opportunity about the benefits of COVID-19 vaccination using a technique I call “The 4 Es” (Table 3).

Psychiatrists who work in integrated care settings, hospitals, and public health clinics are ideally
placed to educate medical colleagues and public health officials about the ethics of COVID-19 vacci-
nation for persons with SMI and SUD. Similarly, local departments of psychiatry and professional societies can provide information explaining that these 2 groups are at elevated risk of COVID-19, and that many individuals within these cohorts—
with appropriate facilitation—will accept the vacci-
nation and should have it offered to them, along with other marginalized populations. 24

As the momentum for mandatory vaccination gathers, psychiatrists have an ethical duty to up-
hold the values of informed consent and autono-

cous decision-making among individuals with SUD and SMI who may be at elevated risk of coer-
cion. 25 For example, generally speaking, vaccina-

tion should not be required for voluntary admis-
sion to a psychiatric hospital or residential treatment program. Instead, staff should work col-

laboratively with the patient to persuade them to understand how vaccination meets their own treat-

ment goals and also protects their fellow patients and caregivers.

Concluding Thoughts

The national vaccine rollout is showing signs of success, even while premature abandonment of public health measures and the growing domi-
nance of variants threatens a fourth wave of infec-
tions. 26 Our advocacy on behalf of our patients and our profession can significantly shift the direction of the pandemic, and even further, set a precedent for the infectious disease outbreaks that are unfor-
tunately inevitable in the future. Securing equity for our patients and ourselves in COVID-19 vacci-
nation is also a critical step in the long and vital walk toward the larger goals of destigmatization and justice in psychiatric care. For patients with

SMI and SUD and those who care for and about them, COVID-19 may fulfill both meanings of a crisis: It is a challenge and an opportunity. The pandemic can serve as professional impetus and ethical rationale to redouble our efforts to achieve equity, so that when the next public health emer-
gency strikes, we are all encompassed in the com-

munity of immunity.

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Table 3. The 4 Es

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Encourage them to consider vaccination
Empathize with their fears and anxieties
Empower them to make a decision that reflects their values and interests

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Table 2. Obstacles to Vaccination (and how to overcome them)

<table>
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<tr>
<th>Obstacles to vaccination experienced by SUD/SMI</th>
<th>Tips for overcoming obstacles</th>
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<tr>
<td>Lack of health literacy about COVID-19</td>
<td>Mental health professionals develop and deliver targeted education about risk of COVID-19 and about protective measures, including vaccination</td>
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<tr>
<td>Vaccine hesitancy, distrust, skepticism</td>
<td>Build on trust of therapeutic relationship</td>
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<td>Difficulties arranging vaccination appointments</td>
<td>Leverage simple technology</td>
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<td>Transportation difficulties</td>
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Table 3. The 4 Es

- Educate yourself, then educate your patients
- Encourage them to consider vaccination
- Empathize with their fears and anxieties
- Empower them to make a decision that reflects their values and interests
Part 1

Sexual and Gender Minorities

The Mental Health of SGM Youth

Embracing Affirmation

Jack Turban, MD

Sadly, psychiatry has a dark history when it comes to the treatment of sexual and gender minority (SGM) individuals. As a gay man, it was disappointing to recognize that our profession classified homosexuality as a mental illness until 1973. The field has similarly—and fairly, I should add—been criticized for inappropriately pathologizing transgender and gender-diverse people.

But I am also proud to say that our profession has made major strides in overcoming its past. The American Psychiatric Association (APA) and the American Academy of Child & Adolescent Psychiatry (AACAP) have unambiguously stated that gender diversity and homosexuality are not pathological, but rather manifestations of healthy diversity. These associations have clearly labelled attempts to force SGM people to be non-SGM (e.g., conversion therapies) as dangerous and unethical. Instead, we have developed protocols that affirm SGM individuals. We have recognized that the primary drivers of mental health problems among SGM individuals are societal stigma and rejection. Along with this recognition, we have started to build evidence-based protocols to help SGM youth build resilience in the face of these unjust adversities.

Politicians have not caught up with the mental health profession. SGM individuals continue to face discriminatory public policies that negatively impact their mental health. One recent example is legislative attempts to outlaw gender-affirming medical care for transgender youth. Although this legislation was opposed by all relevant major medical organizations (the APA, AACAP, and the American Academy of Pediatrics, to name a few), politicians have aggressively pushed these bills forward. In Arkansas, one such bill just became law, putting young people in that state at high risk of mental health crises.

In parallel with these attacks on SGM individuals from politicians, society has seen a resurgence of attacks on SGM individuals broadly, particularly SGM youth. Transgender youth in particular have become targets—with high-profile media outlets pathologizing their identities. Many of us have seen this attitude trickle down to parents, who may come into the clinic noting that they have heard in the news or on television that they should not affirm their transgender children.

It is my hope that politicians and society at large will make the same shifts we made in psychiatry: recognizing that diverse gender identities and sexual orientations should be celebrated and affirmed, not pathologized and attacked. But I also believe that it is the responsibility of every psychiatrist to spread evidence-based information about these populations.

In this Special Report, we focus specifically on the mental health of SGM youth. I hope readers will be inspired by the cutting-edge science and evidence-based recommendations inside this issue. I encourage readers to integrate these lessons into clinical practice, and take an active role in ongoing societal and political discourse so that we can best support these young individuals.

Given the history of harm that psychiatry placed on the SGM community, it is the least we can do to support this vulnerable and marginalized population.

Dr Turban is a fellow in child and adolescent psychiatry at Stanford University School of Medicine, Palo Alto, California, where he researches the mental health of transgender youth. He reports that he receives textbook royalties from Spring Nature, and from expert witness testimony for the ACLU and Cooley LLP. He has received pilot research award for Gender Psychiatry Residents from the American Academy of Child & Adolescent Psychiatry, support by industry donors (Pfizer and Arbor), and is on the Scientific Advisory Board for Panorama Global.
Special Considerations for SGM Youth Online

Mathijs F. G. Lucassen, PhD; and Ana M. Ugueto, PhD, ABPP

Despite rapid social progress, including the landmark United States Supreme Court ruling on same-sex marriage in 2015, challenges remain for young individuals who are lesbian, gay, bisexual, transgender/trans, or queer (also known as sexual and gender minority or SGM youth). Fortunately, since the start of this century, online environments have revolutionized the lives of young SGM individuals, so even those in the most remote of locations can access discrete and timely supports. While the internet has generated many benefits for SGM communities, it has also created new problems, such as the rise of internet-based homo-, bi- and trans-phobic bullying, online sexual exploitation, as well as worrying conversion tactics.

Given the diversity implicit under the wider SGM umbrella, it is important to briefly define these unique subpopulations and their mental health needs before delving into the impacts of online environments for these young people.

Defining Communities
To identify as lesbian, gay, or bisexual (LGB) is to claim a certain, often politicized, sexual identity label. However, sexual attractions and sexual behavior are other important dimensions of human sexuality.1 Depending on the dimension of sexuality assessed, estimates of nonheterosexual prevalence varies considerably, even when estimates are derived from population-based studies.

Assuming questions related to sexuality are included in these large-scale studies, researchers have consistently reported that a substantial proportion of youth identify as being a sexual minority individual. For instance, up to 8% of youth identify as bisexual, and up to 3% of youth identify as lesbian or gay.2 Meanwhile, although being LGB is related to sexuality, being transgender/trans pertains to one’s gender identity. (See Sidebar for more information.)

Mental Health Challenges
Robust population-based data have demonstrated SGM youth are at an elevated risk of a range of mental health problems, including suicide attempts, depression, anxiety, and addiction issues.3,4 Unfortunately, there is limited population-based data focused on the mental health of transgender adolescents.

For instance, a systematic literature review and meta-analysis of suicide attempts among SGM young individuals identified only a single study in which the results for transgender adolescents were presented separately, and not combined together with SGM youth.5 Based on the meta-analysis, transgender adolescents were nearly 6 times more likely to attempt suicide when compared to their cisgender peers.6

The increased rates of mental health problems are hypothesized to be caused by minority stress, whereby the mistreatment associated with the high levels of stress these youth encounter is thought to place them at an increased risk for emotional problems.7,8 Experiencing this mistreatment also results in internalizing the negativity associated with anti-SGM messages, which can lead to mental health issues.

Online Environments
Opportunities for Affirmation and Community
The internet has initiated a revolution for SGM youth because geographic boundaries are no longer limiting: these young people can now connect online with others like themselves. As such, the internet has exerted a powerful influence, with numerous advantages. For instance, those in rural or more socially hostile environments can obtain support via online groups as well as from charitable organizations that provide free online services 24 hours a day, 7 days a week (Table 1). This is a huge advantage. SGM-specific information on relationships and sexual health is also freely available online.

Bullying, Harassment, and Exploitation Risks
Bullying behaviors and trolling via social media platforms are concerning issues in general and especially for SGM youth. It is worth noting that some of this mistreatment can take the form ofhorizontal violence in which one SGM youth bullies another SGM youth. Both young individuals as well as health professionals have previously identified internet safety and security issues being important considerations.9,10 Specific examples include the risk of SGM youth being outed against their will on social media and youth being targeted for sexual exploitation online.11,12 The United Kingdom-based SGM charity, Stonewall, has recently made recommendations to support the safety of youth online.13 Selected top tips from this report are summarised in Table 2.

Risks of Online Conversion Efforts
SGM youth in high-income countries are thought to be coming out at younger ages.14 Consequently, many will still be living at home and will be dependent on their families when they first come out. Unfortunately, not all families will be supportive, and some will actively attempt to secure services and information—either online or face-to-face—aimed at “converting” or “correcting” the SGM youth. This practice still occurs, despite the disapproval of professional bodies toward reparative or conversion therapy, including strong opposition from the American Psychiatric Association14 as well as the American Academy of Child and Adolescent Psychiatry.15

Mental Health Services
The online context is a valuable milieu in which to deliver psychotherapy at the present time, especially for SGM youth because this population has previously indicated a preference for web-based support for mental health issues.16 Yet few evidence-informed interventions have been developed for these youth. Two systematic reviews of psychosocial treatments in the peer-reviewed literature found only a single tested online tool—Rainbow SPARX—to support the mental wellbeing of SGM adolescents.17–21

Rainbow SPARX, a cognitive behavioral therapy program for adolescent depression, has been specially adapted for SGM youth, but it has not been made available to prospective users outside of a research context. The mainstream version of SPARX has been freely available to all youth in New Zealand since 2014. However, SPARX was less effective for transgender adolescents in comparison with other users who did not

Table 1. Resources for SGM Youth, Families, and Professionals

<table>
<thead>
<tr>
<th>For awareness, education, and support</th>
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<tbody>
<tr>
<td>The Trevor Project</td>
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<tr>
<td>Human Rights Campaign</td>
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<tr>
<td>National Gay and Lesbian Task Force</td>
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<tr>
<td>National Center for Transgender Equality</td>
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<tr>
<td>Gay &amp; Lesbian Alliance Against Defamation (GLAAD)</td>
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<tr>
<td>Gender Spectrum</td>
</tr>
<tr>
<td>Family Acceptance Project</td>
</tr>
<tr>
<td>Parents, Families, and Allies of Lesbians and Gays (PFLAG)</td>
</tr>
<tr>
<td>It Gets Better Project</td>
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<table>
<thead>
<tr>
<th>School resources</th>
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<tr>
<td>Gay, Lesbian, and Straight Education Network (GLSEN)</td>
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<tr>
<td>Stomp Out Bullying</td>
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<tr>
<td>Trans Student Educational Resources</td>
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<td>Gender and Sexualities Alliance (GSA)</td>
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<table>
<thead>
<tr>
<th>Educational resources</th>
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<tbody>
<tr>
<td>The Gender Wheel</td>
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<tr>
<td>The Gender Book</td>
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<tr>
<td>The Gender Unicorn</td>
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<tr>
<th>Legal resources</th>
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<tbody>
<tr>
<td>Lambda Legal</td>
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<tr>
<td>Transgender Law Center</td>
</tr>
</tbody>
</table>

Table 2. Top tips from The United Kingdom’s Stonewall

- Keep it safe: Online platforms can be a powerful tool for support and information. However, it is important to consider the potential risks of unknown individuals who may misuse their personal information. It is always wise to keep personal information confidential and not to share it with strangers.

- Be mindful of online contacts: Online environments can be filled with individuals who may not have good intentions. It is crucial to be cautious about who you engage with and to trust your instincts. If something feels off, it is important to take steps to protect yourself.

- Use online resources wisely: There are many online resources available to support SGM youth. However, it is important to use these resources with care and to seek professional help when needed.
Brief Summary of Prescribing Information for Drizalma Sprinkle™
(duloxetine delayed-release capsules). This Brief Summary does not include all the information needed to use Drizalma Sprinkle™ safely and effectively. See full Prescribing Information for Drizalma Sprinkle™.

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS
See full prescribing information for complete boxed warning.
Increased risk of suicidal thinking and behavior in pediatric and young adult patients taking antidepressants.
Closely monitor all antidepressant-treated patients for clinical worsening and for emergence of suicidal thoughts and behaviors.

INDICATIONS AND USAGE
Drizalma Sprinkle™ (duloxetine delayed-release capsules) is a serotonin and norepinephrine reuptake inhibitor (SNRI) indicated for:
• Major Depressive Disorder (MDD) in adults
• Generalized Anxiety Disorder (GAD) in adults and pediatric patients aged 7 to 17 years old
• Diabetic Peripheral Neuropathic Pain (DPNP) in adults
• Chronic Musculoskeletal Pain in adults

CONTRAINDICATIONS
Serotonin Syndrome and MAOIs: Do not use MAOIs intended to treat psychiatric disorders with Drizalma Sprinkle™ or within 5 days of stopping treatment with Drizalma Sprinkle™. Do not use Drizalma Sprinkle™ within 14 days of stopping an MAOI intended to treat psychiatric disorders. In addition, do not start Drizalma Sprinkle™ in a patient who is being treated with linezolid or intravenous methylene blue.

DOSAGE AND ADMINISTRATION
• Drizalma Sprinkle™ can be taken with or without food. Drizalma Sprinkle™ may be swallowed whole (do not crush or chew capsule); opened and sprinkled over applesauce; or administered via nasogastric tube
• Missed doses should be taken as soon as it is remembered. Patients should not take two doses of Drizalma Sprinkle™ at the same time
• There is no evidence that doses greater than 60 mg/day confers additional benefit, while some adverse reactions were observed to be dose-dependent

WARNINGS AND PRECAUTIONS
• Hepatotoxicity: Hepatic failure, sometimes fatal, has been reported in patients treated with duloxetine delayed-release capsules. Duloxetine delayed-release capsules should be discontinued in patients who develop jaundice or other evidence of clinically significant liver dysfunction and should not be resumed unless another cause can be established. Drizalma Sprinkle™ should not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease
• Orthostatic Hypotension, Falls, and Syncope: Cases have been reported with duloxetine delayed-release capsules therapy
• Serotonin Syndrome: Increased risk when coadministered with other serotonergic agents (eg, SSRI, SNRI, triptans), but also when taken alone. If it occurs, discontinue Drizalma Sprinkle™ and initiate supportive treatment
• Increased Risk of Bleeding: Duloxetine may increase the risk of bleeding events. A post-marketing study showed a higher incidence of postpartum hemorrhage in mothers taking duloxetine. Concomitant use of NSAIDs, aspirin, other antiplatelet drugs, warfarin, and anticoagulants may increase this risk

• Severe Skin Reactions: Severe skin reactions, including erythema multiforme and Stevens-Johnson Syndrome, can occur with duloxetine. Drizalma Sprinkle™ should be discontinued at the first appearance of blisters, peeling rash, mucosal erosions, or any other sign of hypersensitivity if no other etiology can be identified
• Discontinuation Syndrome: Taper dose when possible and monitor for discontinuation symptoms
• Activation of Mania or Hypomania: Use cautiously in patients with bipolar disorder. Cautions patients about the risk of activation of mania/hypomania
• Angle-Closure Glaucoma: Avoid use of antidepressants, including Drizalma Sprinkle™, in patients with untreated anatomically narrow angles
• Seizures: Prescribe with care in patients with a history of seizure disorder
• Blood Pressure: Monitor blood pressure prior to initiating treatment and periodically throughout treatment
• Hyponatremia: Can occur in association with SIADH. Cases of hyponatremia have been reported
• Glucose Control in Diabetes: In diabetic peripheral neuropathic pain patients, small increases in fasting blood glucose and HbA1c have been observed

ADVERSE REACTIONS
Most common adverse reactions (≥5% and at least twice the incidence of placebo patients) nausea, dry mouth, somnolence, constipation, decreased appetite, and hyperhidrosis.

DRUG INTERACTIONS
• Potent CYP1A2 Inhibitors: Avoid concomitant use
• CYP2D6 Substrates: Consider dose reduction with concomitant use

USE IN SPECIFIC POPULATIONS
• Hepatic Impairment: Avoid use in patients with mild, moderate, or severe hepatic impairment
• Renal Impairment: Avoid use in patients with severe renal impairment
• Pregnancy: Third trimester use may increase risk of symptoms of poor adaptation (respiratory distress, temperature instability, feeding difficulty, hypotonia, tremor, irritability) in the neonate. Advise patients that Drizalma Sprinkle™ use during the month before delivery may lead to an increased risk for postpartum hemorrhage and may increase the risk of neonatal complications requiring prolonged hospitalization, respiratory support and tube feeding.
• Lactation: Advise breastfeeding women using duloxetine to monitor infants for sedation, poor feeding and poor weight gain and to seek medical care if they notice these signs.

To report SUSPECTED ADVERSE REACTIONS, contact Sun Pharmaceutical Industries, Inc. at 1-800-818-4555 or FDA at 1-800- FDA-1088 or www.fda.gov/medwatch.
Please read full Prescribing Information and Medication Guide for Drizalma Sprinkle™ and discuss any questions with your doctor.

Manufactured by:
Sun Pharmaceutical Industries Limited,
Mohali, INDIA

Distributed by:
Sun Pharmaceutical Industries, Inc.
Crabury, NJ 08512

PM-US-DRI-0099
identify as transgender.23 The results suggest targeted efforts are needed to address the mental health needs of SGM youth.

**Concluding Thoughts**

The internet is both ubiquitous and influential. SGM youth have grown up with modern technologies in a way that their caregivers and clinicians have not. As such, it is important that clinicians defer to their expertise as digital natives and remain open-minded about online environments as they proffer many benefits. Clinicians also need to be nonjudgmental and aware of the considerable challenges facing SGM youth online, so that SGM youth will discuss their concerns with their clinicians as these arise. In addition, treatment providers should encourage their SGM youth patients to maximize the benefits from their online experiences while managing the potential risks or challenges. We anticipate more work will be undertaken in the fields of cognitive-behavioral therapy and e-therapies for SGM youths.

### Table 2. Tips Communicating With Young Patients

<table>
<thead>
<tr>
<th>Top tips*</th>
<th>What this entails</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use the internet for all the right reasons</td>
<td>The internet can be used for a range of positive purposes, from raising money for charity to sharing posts from other SGM youth doing great things, or simply for sending a friend an amusing photo to cheer them up when they are down.</td>
</tr>
<tr>
<td>Report online bullying and mistreatment</td>
<td>If someone is treating an SGM young individual unkindly online and/or not respecting them for who they are, encourage the young individual to report this behavior.</td>
</tr>
<tr>
<td>Ask if it is OK to do</td>
<td>Encourage the youth to reflect upon how their own online actions might make others feel. Obtain permission before posting a picture with others, or before adding others into group chats.</td>
</tr>
<tr>
<td>It is important to keep personal information safe</td>
<td>Personal information includes SGM status, full names, date of birth, addresses, and passwords.</td>
</tr>
<tr>
<td>Think before posting</td>
<td>Consider the possible consequences of online actions, because a posting can be seen by a lot of individuals. Sometimes, for reasons of self-preservation, an SGM young individual may be better off not commenting on certain posts in unsupportive forums.</td>
</tr>
<tr>
<td>Think critically</td>
<td>Not all information on the internet is trustworthy or helpful. Youth should use their critical thinking skills, as well as the support of those around them, to figure out what is reliable, helpful, and good for their mental health.</td>
</tr>
<tr>
<td>Not everyone is who they say they are online</td>
<td>Youth should seek advice from a trusted adult if anyone (only known to the youth online) makes them feel uncomfortable, or asks to meet up or share personal information, including images.</td>
</tr>
<tr>
<td>Talking helps</td>
<td>Talking to a trusted individual (especially if something happens online that makes the youth feel worried, upset, or confused) is important.</td>
</tr>
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</table>

*Tips derived from the Staying Safe Online report

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**What Constitutes an SGM Community?**

**Mathijs F. G. Lucassen, PhD; and Ana M. Ugueto, PhD, ABPP**

In the academic literature the terminology “sexual and gender minority” or SGM is commonplace. That is because SGM helps to succinctly encapsulate a diverse range of people, who often identify with multiple SGM identities. However, it is rare for young people to refer to themselves as SGM, instead (as summarized below) LGBTQ+ terms are more likely to be used.

Typically, when an individual’s sex assigned at birth differs from their gender identity (ie, how they know themselves to be), they are categorized as transgender or gender diverse.2 Thus, an individual assigned male at birth who identifies as female is frequently described as a trans girl or trans woman (or simply just as a girl or woman). Individuals who identify as non-binary (ie, not exclusively masculine or feminine identified) are also gender diverse, as they fit outside the male/female gender binary. Conversely, a young individual whose sex assigned at birth directly aligns with their gender identity is usually described as cisgender. Based on population-based data and other study estimates, approximately 1% of young individuals are transgender.3,4

It is important to note that LGBTQ+-related labels and terms continue to evolve. For instance, there has been some debate about whether or not the more established sexual identity labels (ie, gay, lesbian, and bisexual) have now lost their meaning and relevance resulting in young people today being post-gay.5 These old labels still appear to be of value for the majority of sexual minority youth,6 alongside the meanings ascribed to more contemporary terms such as “pansexual” (ie, attraction regardless of assigned sex or gender identity), “querer” (a reclaimed word), or developmentally relevant terms such as “questioning.”

Other unique subpopulations, which at times are grouped under the “plus” in LGBTQ+, include asexual and intersex individuals. Asexual individuals are those who lack sexual attractions to others. In the case of adolescents, however, it is important to consider developmental factors. For example, younger teenagers may report being “neither sex attracted.” This does not necessarily mean that they are asexual per se, but rather with age many are likely to start experiencing sexual attractions.4 Intersex individuals are born with biological or physical sex characteristics (eg, sexual anatomy and hormonal variations) that are more diverse than those stereotypically linked to male and female bodies. Consequently, they are diverse in terms of their sex.

LGBTQ+ youth are also diverse in terms of other important demographic features, such as being from a racial, ethnic, or religious minority group, having a disability, having an overlapping identity (like being LGB as well as transgender), or any combination of these features.7 Unfortunately, there is still stigma associated with being anything other than exclusively heterosexual and cisgender.2 As a result, LGBTQ+ youth often remain hidden (what is known as “in the closet”) and subsequently can be hard to reach.

Language does matter, and although “sexual and gender minority” terminology is useful, particularly in the academic literature, it tends to be “technical jargon” that is not in common usage. When working with SGM youth, it is therefore important to pay attention to the labels and their associated descriptions, as these are used by the young person. This also extends to using the patient’s correct pronouns (ie, she/her, he/him or they/them), as indicated by the young person.

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**REFERENCES**

2. Turban JL, Ehrensaft D. Research review: gender identity, “queer” (a reclaimed word), or developmentally relevant terms such as “questioning.”
The Negative Impact of Current Legislation on Gender Diverse Adolescents

"Jessica," a 13-year-old transgender girl, lives in a rural community where no other individuals identify as transgender. She has a supportive family and was able to safely come out to her parents. She socially transitioned 2 years ago. Despite support at home, Jessica and her family have faced challenges at school. The other teens in her grade did not accept her when she came out. They started to call her names such as "she-male" or "it." She started feeling depressed and avoiding school. Her parents inter- vened and spoke with a counselor at school. The counselor remembered a training by the State Department of Education where they discussed a comprehensive bill supporting transgender youth. The school was required to educate staff and eliminate any discrimination. The teachers were given resources to help them better understand Jessica’s journey, and those resources helped them support her better. The bullying decreased and Jessica’s depression, anxiety, and school attendance improved.

"John," a 16-year-old transgender boy, lives in a large city and recently started high school. He received a diagnosis of depression and has had 2 hospital admissions for suicide attempts beginning at age 12. He has explored his gender over the past 3 years and came out to his parents a year ago after discussing it with his therapist and psychiatrist, both of whom have been supportive. The treating team was able to help his parents learn about John’s gender development, and his parents also became supportive.

Unfortunately, John’s school has been a major stressor for him. He was bullied for being a tomboy at school and is scared to come out. He wants to start testosterone treatment but fears a negative reaction from his peers. His parents have spoken to the school, asking administrators to help with his transition and provide a safe environment to come out.

One of the parents of another student who was involved in bullying John raised issues with his transitioning and referred to the recent bill that their state passed, which bans transgender children from using their bathroom of choice. John has been holding his urine at school until he gets home. His depression escalated, and his grades dropped. His family is struggling to find a safe environment for him.

Gender-diverse individuals have been marginalized and discriminated against in many communities throughout history. Modern psychiatry initially adopted a pathological view of transgender identity as well. However, the work of human rights advocates, supported by growing medical evidence, has caused medical and health care organizations to reverse their discriminatory stances against transgender individuals over the past few decades. Compelling evidence shows that transgender identities or nonconforming gender presentations are not pathological nor indicate a disorder. These individuals may require medical interventions to stop the course of endogenous pubertal changes in order to match their desired gender identity, as outlined in guidelines from the World Professional Association for Transgender Health Standards of Care and Endocrine Society.

It is well established that discrimination negatively impacts transgender and gender-nonconforming youth. The rate of depression and anxiety among transgender and gender-nonconforming youth is several times higher than the rate of their cisgender peers. These youths are more likely to seriously consider suicide or illegally use substances. These effects are mainly due to structural discrimination, both in society’s attitudes and the legislative system. Coercive interventions that even try to alter gender identity, sometimes called “conversion therapy,” are harmful and ineffective.

Lack of school belonging as well as interpersonal microaggressions have been shown to be directly linked to suicidality and lifetime suicide attempts. Conversely, simple acts of affirmation have demonstrated profound positive effects. Even the repeated use of a transgender or gender-nonconforming youth’s chosen name can reduce suicidal thoughts and behavior. The more widely it is used, the stronger the effect.

The positive effects of gender-affirming care on transgender or gender diverse youth are similarly well-documented. Gender-affirming care improves positive mental health outcomes, and youth who receive it are less likely to attempt suicide. Pubertal suppression decreases depressive symptoms, as well as behavioral and emotional problems. Likewise, gender-affirming hormone therapy also decreases behavioral and emotional issues and improves body image and psychological well-being.

Recently, Jessica began puberty. She is not certain whether she wants to take gender-affirming hormones. Her family physician recommended that Jessica and her family speak with an endocrinologist. Jessica’s town does not have an endocrinologist. In fact, the nearest endocrinologist is Dr Sanchez, whose practice is about an hour away.

Figure. Antitransgender Bills Across the United States 2021

<table>
<thead>
<tr>
<th>State</th>
<th>Number of Bills</th>
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<tbody>
<tr>
<td>California</td>
<td>8</td>
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<tr>
<td>Texas</td>
<td>10</td>
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<tr>
<td>Florida</td>
<td>5</td>
</tr>
<tr>
<td>Washington</td>
<td>2</td>
</tr>
<tr>
<td>New York</td>
<td>1</td>
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Currently there are at least 43 youth antitransgender bills across the United States. Source: freedomforalloamericans.org
The rights of transgender youth have become a battleground for political agendas at the intersection of structural discrimination and gender-affirming care. Dozens of states have proposed bills that would criminalize gender-affirming care (Figure). Doctors who perform this care would be subject to fines, imprisonment, or even loss of license. Laws criminalizing gender-affirming care are a major legislative theme this session, but dozens of other antitransgender bills join them. Currently there are more than 45 such antitransgender bills in local governments across the United States, following failed proposal bills in several states last year and similar so-called “bathroom bills” over previous years. A majority of these bills seek to deny transgender youth access to treatments that could help them feel more comfortable with their bodies. The stories of Jessica and John are the same stories of hundreds of thousands of youth in the United States. Child psychiatrists and other mental health professionals are treating many of these youth. Their presentation can be complex, and treatment requires an in-depth understanding of their gender development, family dynamics, and psychosocial environment. Care can also be further complicated by state legislation. Physicians and other health care professionals are bound ethically not to harm their patients and provide medically necessary services to help them. Discriminatory bills, such as those proposed where John lives, can create a conflict for health care professionals between medically appropriate care and legally acceptable guidelines. Although some think that delaying affirmative care until the age of majority is a harmless option, there is solid and growing evidence that affirmative care improves a transgender youth’s mental health.

Establishing good mental health for a transgender youth often starts from a nucleus of support, whether that is in the home, the school, or a close group of friends. This support can buffer these youth from the negative impacts of antitransgender legislation. As in the care of many other youths, identifying ways to increase available support or add additional support provides significant benefit to overall psychological well-being. Psychiatrists can be a part of that nucleus of support for these youth.

In a more active role, doctors can be crucial in advocating for the well-being of transgender youth. Major medical and health care associations have local organizations in each state. Educating members of these organizations and mobilizing them to advocate against discriminatory bills can be an important tool to help youth like John, whose life can change significantly with a single law. As such, it is vital that advocates call state representatives when antitransgender legislation is introduced. If mental health experts do not educate legislators on the mental health impacts of these bills, no one else will. Psychiatrists have a duty to patients that goes beyond the boundaries of the office; in some instances, the ethical dilemmas may help psychiatrists recognize the need to raise their voices and stand up for their patients (Table).

Concluding Thoughts

There is much that psychiatrists and other mental health professionals can do to support transgender youth patients: donate time or money to organizations that support transgender youth; speak and advocate for transgender youth by working with state professional organizations; call state legislature representatives when antitransgender legislation arises, highlighting the adverse mental health impacts such legislation would cause; and help establish more support at the family and school level.

Dr. Chavez is a psychiatrist in the United States Department of Veterans Affairs’ newly created Lesbian, gay, bisexual, transgender, queer specialty service in Colorado. Dr. Shadianloo is a clinical assistant professor of psychiatry at the Donald and Barbara Zucker School of Medicine at Hofstra/Northwell.

REFERENCES
Partnersing for the Greater Good

Sara Robinson, MSN, RN, PMHNP-BC

A report published by the United States Department of Health and Human Services Health Resources and Services Administration projected that the mental health care field will be short 250,000 mental health professionals by 2025. The need is most significant in rural areas, where 111 million Americans currently reside. For instance in New Hampshire, where I live and practice, there are significant shortages of psychiatrists and other mental health care providers. With the rise in the number of psychiatrists reaching retirement age, the reviewer indicated the decision was made to deny the medication for one reason: I was a nurse practitioner. As such, the reviewer added, it was his opinion that my assessment was invalid based on my credentials and could not be used to justify the use of this medication.

I was stunned, speechless, and angry. I understand not everyone will support my professional role, but I would not allow a misunderstanding about scope of practice and this individual’s bias to interfere with appropriate patient care and the patient’s best interest. By denying the medication coverage, they were not hurting me, they were hurting the patient. That was something I could not—and would not—let go.

What was my next stop? I visited my colleague, a psychiatrist. I explained the situation, and he jumped right into action to assist me in achieving a resolution. As it turned out, the previous conversation was recorded; it was clear what had happened. The outcome was the only reasonable one. The patient’s medication was covered for the next few years.

Teams for Success

Working in mental health is not the average career in which you go home and share what happened.

On Becoming a PMHNP

Hildegard Peplau, the founder of advanced practice psychiatric nursing, was a nurse theorist and educator, and her development of the theory of interpersonal relations revolutionized nursing care. Peplau collaborated with Harry Stack Sullivan, MD, renowned for his contributions to interpersonal approaches to treatment and his publication of The Interpersonal Theory of Psychiatry. Peplau developed and implemented the first master’s-level role for advanced practice nurses to provide direct care to psychotic patients. The advanced practice role shifted from clinical nurse specialist to advanced practice registered nurse in the early 1990s. Today, students who have successfully completed an accredited program are eligible to sit for the board certification exam through American Nurses Credentialing Center to obtain PMHNP certification.

Education is an ongoing process, however, and does not end with board certification. Board-certified PMHNPs are required to renew national certification every 5 years and must complete 75 continuing education units. In addition, nurse practitioners maintain certification by remaining active in clinical practice and completing additional renewal requirements in domains that demonstrate continued competence. Additionally, all PMHNPs must meet specific state-level requirements for maintaining state licensure as both a registered nurse and a nurse practitioner; many states require renewal of these licenses every 2 years. PMHNPs also have years of experience as professional nurses, which serve to hone their clinical judgment and assessment skills. The hands-on clinical experience of interacting with patients during prelicensure education, clinical practicum, and subsequent practice is a valuable asset. Therapeutic communication is a core skill, and the therapeutic relationship with patients is a central tenet throughout all levels of training, especially within psychiatric nursing.

Practice authority for nurse practitioners varies from state to state, ranging from full practice to reduced or restricted practice. Many states require collaboration, supervision, or consultation with a physician for nurse practitioners to practice. Even in states without a collaborative requirement, many nurse practitioners choose to participate in formal and informal supervision with physician colleagues. Massachusetts recently joined the rest of the New England states by passing legislation to grant nurse practitioners full practice authority, becoming the 23rd state to do so.

Ms Robinson is a psychiatric mental health nurse practitioner in the Seacoast, New Hampshire area, and clinical assistant professor and program director of the Post-Masters Psychiatric Mental Health Nurse Practitioner Certificate Program, Department of Nursing, University of New Hampshire, Durham.

REFERENCES
“As John J. Miller, MD, wrote in a recent editorial, we are all part of a team facing the monumental task of meeting the mental health needs of all Americans.”

Every PMHNP takes a unique path to the specialized education, training, and subsequent national certification to practice (Sidebar). Although our journeys may be different, we value hearing about our psychiatrist colleagues’ experiences. In the community mental health center setting, I enjoyed opportunities for formal and informal supervision with my psychiatrists, and we had been able to support one another throughout work and beyond. Although I no longer work in this position, I remain in contact with both psychiatrist and nurse practitioner colleagues. There is a bond that is difficult to define or put into words. Sharing a purpose beyond. Although I no longer work in this position, I only considered positions that offered formal supervision, even though I practiced in an independent-authority state. The position I chose had the best setup for me as a physician and my colleagues at any time. One such colleague was Miller, who is Editor-in-Chief of this publication. I am incredibly lucky to have him as a resource and a mentor, along with the other wonderful clinicians and psychiatrists with whom I have had the opportunity to work.

Learning is a lifelong process, and the ability to continue to be receptive to new information and feedback is crucial for all clinicians. PMHNPs greatly value our collaboration with physicians and appreciate the many psychiatrists who have offered their expertise and time to PMHNP students and PMHNPs in clinical practice via formal or informal collaboration and supervision, mentorship, and support. I have been particularly fortunate to work with supportive psychiatrists over the years, some of whom remain close friends.

Looking Forward
I am excited to be part of the Psychiatric Times team and look forward to providing an avenue for the voice of fellow nurse practitioners. Many PMHNPs and psychiatrists are already collaborating well, but I hope to facilitate even more nurse practitioner contributions and PMHNP-psychiatrist partnerships. Here’s to the start of more beautiful collaborations.

Ms Robinson is a psychiatric mental health nurse practitioner in the Seacoast, New Hampshire, area and clinical assistant professor and program director of the Post-Masters Psychiatric-Mental Health Nurse Practitioner Certificate Program, Department of Nursing, University of New Hampshire, Durham.

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A Pioneer of Psychosomatic Medicine

Robert M. Kaplan, MBChB, FRANZCP, MA, MPhil

The history of psychiatry does not lack for great names. One of the greatest must be Helen Flanders Dunbar, MD, PhD. Widely recognized as the prime mover behind the psychosomatic medicine movement, she was a clinician, writer, the inaugural editor of *Psychosomatic Medicine*, and founder of the American Psychosomatic Society. In addition, Dunbar’s work was essential to the development of consultation-liaison psychiatry. She also dedicated her professional life to promoting the role of clergy in medicine and exploring accident proneness. She lived a full, brilliant, and ultimately tragic life.

Born May 14, 1902, Dunbar came from a professional family. Her father was a mathematician, engineer, and patent attorney; her mother a genealogist; and her brother, Francis, earned a master’s degree in botany at Stanford University. She, too, received a remarkable education. At Bryn Mawr College and Columbia University she majored in mathematics and psychology. She then went on to earn 4 advanced degrees in 7 years. Dunbar attended Yale School of Medicine for medicine and obstetrics. She wrote a doctoral thesis on Dante at nearby Union Theological Seminary.

Her Episcopalian faith was a guiding light in her life, and she believed it should inform her medical practice. Dunbar worked closely with Anton Boisen, a clergyman inpatient at Westboro Mental Hospital who was convinced that religion and psychiatry needed to be connected on a professional level. Together they trained ministers to work in medical settings.

In 1929, Dunbar broadened her medical and spiritual horizons by traveling to Europe. She met the day’s leading figures in psychiatry and visited Lourdes, the world’s most famous healing shrine in France. This visit had a profound spiritual effect.

She legally changed her name to Flanders Dunbar in 1938. It is disappointing that such an accomplished woman had to change her name to overcome the prevailing misogyny.

From 1930 to 1942, Dunbar was the medical director of the Council for Clinical Training of Theological Students and director of the Joint Committee on Religion and Medicine. During this time, she earned the sobriquet of “mother of holistic medicine” with her 1935 publication of *Emotions and Bodily Changes: A Survey of Literature on Psychosomatic Interrelationships: 1910–1933*. In 1939, she became the first editor of the journal *Psychosomatic Medicine*.

American psychosomatic medicine was born in the 1930s. According to this school of thought, illnesses arose from the physiological effects of emotional stimuli. It was thought that certain psychodynamic patterns created typical illnesses, known as organ specificity. Repressed (and forgotten) emotions emerged from the unconscious to target specific organs, producing psychosomatic disorders. Somatic dysfunctions thus arose from patients’ emotional problems, which led practitioners of psychosomatic medicine to search for psychological profiles characteristic of specific syndromes. This expanded further to the belief that many diseases were psychogenic in origin and stressors, albeit undefined. Dunbar believed that having accidents was similar to the process by which other patients transformed psychological conflicts into somatic symptoms. Their personality styles and neuroses translated into accident proneness.

After 1939, Dunbar gave up academic commitments, drank heavily, alienated followers, and left the American Psychosomatic Society. On August 22, 1959, the publication day of her landmark book *Psychiatry in the Medical Specialties*, she drowned in her swimming pool.

Marcia Dunbar Soule, Dunbar’s daughter, referred to her mother as “a magnetic, charismatic woman with a disturbed and beautiful soul and an almost magical gift of insight and intuition.” It is difficult to put it any better, only to reflect that the passage of time may vindicate more of the views Dunbar held.

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Clinical Dilemmas: What’s Good for the Brain Is Good for the Heart

Lawson Wulsin, MD; and Juliana Zambrano, MD

Treating depression in the context of any other medical disorders can challenge our usual approaches and frustrate our efforts to reach good outcomes. Not surprisingly, this is especially true for patients with depression and coronary heart disease (CHD). For example, how should we screen for CHD risks in our patients with recurrent depression? Does it matter which came first, the depression or the heart disease? What is next for patients who do not respond to the second or third antidepressant trial? How does relapse prevention for depression in patients with CHD differ from relapse prevention in those with depression alone?

Guiding Pearls From Epidemiology
Psychiatric epidemiology over the past 10 years has given us some useful guideposts for approaching patients with comorbid depression and CHD.

PEARL 1: Psychosocial factors, especially recurrent depressive symptoms, severe mental illness, and high numbers of adverse childhood experiences, contribute substantially to both the onset and progression of CHD. The effect size of these psychosocial factors is as strong as that of the traditional CHD risk factors, such as smoking and high cholesterol. Since there is no single cause of CHD, it is helpful to consider psychosocial risk factors among the many contributing influences that determine the course of CHD. The more effectively these psychosocial factors are managed, the fewer hurdles patients will face.

PEARL 2: The large number of psychosocial risk factors for CHD represent the many faces of autonomic imbalance, hypothalamic-pituitary-adrenal axis dysregulation, and/or low grade inflammation. Each of these pathways reflects chronic dysregulation of the stress response system. High risk health behaviors common in depression, such as smoking, physical inactivity, and high-carbohydrate diets, add to this dysregulation process. Effective treatment of depression in patients at risk for CHD includes reducing these early indicators of metabolic syndrome.

PEARL 3: Patients with depression and elevated cardiac risk factors can often be identified in their 30s and 40s, a prime opportunity for preventive interventions in the context of depression treatment and relapse prevention. For patients with recurrent depression, psychiatrists can play an essential role, offering both early identification of CHD risks and behavioral interventions for CHD risk reduction.

PEARL 4: The most robust psychosocial interventions for CHD are intensive lifestyle medicine programs. Psychiatrists can motivate patients with depression to engage in and sustain these behavior changes.

The Figure summarizes the pathways by which depression leads to adverse cardiac outcomes, and it suggests a framework for approaching common dilemmas in assessment and treatment.

Assessment Dilemmas
“Norma,” a 34-year-old single Black woman comes to see you after her third panic attack on the job as a high school history teacher. She is most concerned about the cat calls and notes passed around by 3 senior athletes insinuating she is gay, which she finds threatening and humiliating. She scores 18 on the Patient Health Questionnaire-9 (PHQ-9). Her history reveals at least 2 other episodes of depression lasting several months at ages 18 and 23, both of which resolved without treatment.

Psychiatrists should consider these important questions as they move forward with such a case (Table):

1. When to dig? More digging may illuminate underlying and complicating issues that need to be considered to develop a successful treatment plan.
2. Which came first? The interrelationship and how one disorder impacts the other is an important consideration in understanding the issues at hand and implementing a treatment plan.
3. What to monitor? The preceding questions should lead to this important query. Based on the issues uncovered, it should become obvious which cardiac and depressive symptoms should be monitored to ensure a successful outcome.

Do we keep treatment simple, ie, treat her with sertraline, and see what happens? Or do we dig and look for potential complications? Norma’s blood pressure is 135/90, and her resting heart rate is 88, both of which she attributes to her being nervous about the appointment. Further probing reveals she has had high blood pressure readings at 2 gynecology visits for birth control pills in the past 2 years, but it has never been addressed. Her BMI is 29, and her mother developed diabetes at age 46. A metabolic panel ordered at your first visit confirms she has high low-density lipoprotein and, therefore, metabolic syndrome (3 of 5 risk factors for CHD).

On her second visit, you press Norma to return to her gynecologist or establish a relationship with a primary care clinician. In addition to a trial of sertraline, you devote some of each monthly appointment to helping her understand how untreated depression accelerates the development of common risk factors for heart disease. At first, she is alarmed. But eventually Norma is motivated to walk to work instead of riding the bus and give up sweetened drinks, 2 behavior changes that are good for her limbic system as well as her heart.

In most individuals the age of onset for depression appears to prece the age of onset for CHD by about 30 years. But Norma’s case reminds us that the underlying processes for each illness may begin much closer in time for many individuals. These 2 illnesses, recurrent depression and CHD, may be driven by shared genetic vulnerabilities to stress. The bidirectional relationship between depression and CHD—each illness raises the risks for the other—means that we should always suspect that in a given patient the occurrence of 1 illness may accelerate the development of the other. It is also safe to assume that effective treatment of either illness facilitates the treatment or prevention of the other illness. For psychiatrists, this translates into the necessity of effective collaborations with primary care clinicians and cardiologists. It is easier to reverse the course of cardiac risk factors when treated early, compared to reversing them after the first heart attack.

Systematic symptom monitoring for depression is especially helpful in the context of physical illnesses symptoms that overlap with depressive symptoms. Serial assessments of depressive symptoms with a PHQ-9 or similar measure improves the efficiency of antidepressant treatment trials. It also charts the relationship between depressive symptoms and the target physical measures of CHD. For example, effective treatment of Norma’s panic attacks and depression may reduce her resting heart rate and her need for antihypertensive medication, or it may not. Serial monitoring of both
targets is the most efficient way to estab-
lish the relationship between these di-
mensions of the 2 illnesses.

Treatment Dilemmas
Choosing a treatment option can be guided by a few considerations, such as previous responses, side effects, and genetic drug metabolism profiles. In the absence of any evidence pointing to or from a specific strategy, the serotonin reuptake inhibitors (SSRIs) sertraline and citalopram have the broadest research base from clinical trials of antidepressants in patients with CHD, are well tolerated, and have the fewest clinically relevant drug interactions. There is also some evidence that SSRIs may provide a protective anti-inflammatory effect in patients with major depression. Serotonin-norepinephrine reuptake inhibitors (SNRIs) are second tier choices only because of their smaller research base. The atypical antidepressant mirtazapine carries a heavier risk for metabolic burden, while buspirone may be a first choice for patients who smoke or those who need management of CHD is undermined as a pivotal period in the life course: balancing growth and decline at the crossroads of youth and old age. The relief and sense of emancipation from depression is an investment that may require a care manager or a structured, daily self-management plan. Periodic checkups at 6- or 12-month intervals can verify which plans are working and which are not. Concluding Thoughts
Treating depression in people with CHD can be tricky and pose complicated dilemmas. It is reassuring to remember that, in spite of all the dilemmas, guidelines to treat these patients boil down to a simple maxim: what is good for the brain is good for the heart.

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Reflecting on Psychiatry’s Role in Religion

Omar Reda, MD

For the most part, the field of psychiatry has looked at organized religions with suspicion, however, a majority of sacred texts have paid particular attention to emotional wellness and holistic health.

I have used my religion and my Muslim background as a grounding and healing tool for myself, my family, my small community, and for clients who requested to use God’s words (the Noble Quran) and the authentic teachings and traditions of Prophet Muhammad (peace be upon him) as part of our therapeutic relationship.

It is usually much easier to introduce religious themes with terminology like spirituality and tending to the soul. Youth in particular seem to have a difficult time reconciling the religious aspect of their personality with societal expectations. I have queried Muslim youth and their caregivers, but my understanding from Jewish and Christian friends and colleagues is that there are similar themes in all 3 monotheistic religions. However, most of the Muslim community’s negative feelings around Islamic organizations and places of worship comes from a heavy legacy of trauma, caused mainly by the culture of the
leadership and from the out-of-context quoting and misinterpretation of a sacred text.

Psychiatrists can bridge gaps between the community and religious leaders through psychosocial education that targets stigma, which in turn helps with opening channels of communication and building bridges of trust.

For instance, look at some of the most widely criticized areas of Islamic centers:

1. A lack of trust between the community and its leaders.
2. A lack of demographic diversity and representation, especially in positions of leadership.
3. Systemic exclusion of certain sectors of the community.
4. A lack of attractive alternatives to the mainstream culture, especially for the youth.
5. Gross violations of the rights of some worshippers, like those with mental disabilities.
6. A lack of transparency and a culture of secrecy.
7. Stigma about psychosocial needs.
8. A culture of competition, rather than collaboration.
9. Poor interfaith and outreach to the larger non-Muslim community.
10. A lack of flexibility of policies and procedures.
11. Harsh approaches in providing and receiving advice and feedback.
13. Not taking advantage of the talents, skills, and expertise of most worshippers.
14. Poor sustainability of programs and resources.

As a kickoff to Spring, Psychiatric Times™ featured a dynamic set of articles acknowledging the importance of environmental protection, the effect of toxic exposures on mental health, and the interplay between the disrespect of cultures, peoples, and our planet. We assembled a collection of contributions for the first-ever Earth & Psychiatry series, as well as a Racism & Climate Change series, both in honor of Earth Day.
16. Spreading a punitive message of despair, rather than advocating for hope and beauty.
17. Weak societal impact, possibly stemming from the attitude of “going back home one day.”
18. Rigid adherence to a certain style or school of thought.
19. Rare access to new blood and young leaders who speak the cultural language.
20. Poor understanding of the American cultural norms, laws, and systems.
21. Poor intrafaith dialogue.
22. Misusing religion to justify dysfunctions like domestic violence and child abuse.
23. Double standards when treating men and women, and boys and girls.
24. Minimal representation of Muslims in the media and in politics.

I have been blessed to earn the trust of both the Imams and the Muslim community in Portland, Oregon, and it is now common to hear discussions inside the house of God about family dynamics, self-care, emotional intelligence, trauma healing, suicide prevention, and many other psychosocial topics that were otherwise censored.

In Islam, the relationship between the Creator and His creation is a personal and intimate one; the face of God can be seen not only in the mosque, but in every beautiful act of kindness toward others. Ultimately, the best way to worship is to serve humanity.

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Helping LGBTQ Youth During the Pandemic

As the number of COVID-19 cases in the United States hits 30 million and continues to cause widespread pain in lives lost and economic devastation, sexual and gender minority youth face particular hardships threatening their lives, mental health, and social development.

In particular, social isolation may be especially challenging. These youths may be quarantining with rejecting family members and losing contact with supportive social networks. The nature of quarantining means these problems are invisible to the public.

“Aiden,” a 16-year-old boy who is transgender, lives in a community particularly hard-hit by COVID-19. Aiden’s parents refuse to accept his gender identity or call him by his male name or use male pronouns. They frequently yell at Aiden to dress and act like a girl, assigning dishwashing and laundry chores to him alone, and not to his brother, to get him “used to doing girl stuff like you are supposed to.”

Serial COVID-19 outbreaks at Aiden’s school forced him into remote learning. His family has only 1 computer, shared by Aiden and his brother for schoolwork and Aiden’s mother for church meetings. Aiden’s parents banned him from using social media or communicating with friends because his parents believe “that’s where she picked up all this nonsense.” Aiden became completely disconnected from his friends. He was also cut off from affirming and supportive teachers. As tensions in Aiden’s family escalated, fighting became the only interaction between him and his parents.

One evening during a fierce argument, Aiden’s mother pushed him, and he pushed her back. As a result, she fell and had a small laceration on her shoulder. Aiden’s father became angry and punched Aiden in the face. Aiden’s brother called 911. The police arrested Aiden and his father. Aiden was released from jail to a Child Protective Services emergency residence. Because of COVID-19, he was required to spend 14 days isolated in his room, including mealtimes, and was unable to receive visitors. He also faced misdemeanor charges for assaulting his mother. His father also faced charges. Aiden was afraid of returning home because he was petrified of what his father might do to him.

Administration for Children’s Services (ACS) attempted to reunify Aiden with his parents, but over a period of several months, each attempt resulted in further physical altercations between Aiden and his father. Aiden moved into a group home where peers bullied him because of his gender identity. ACS was unable to address the problem because several staff members were hospitalized with COVID-19, and no other group homes were available for transfer. After a bully hit him, Aiden ran away from the group home, and the police could not locate him.

Even before COVID-19, lesbian, gay, bisexual, transgender, questioning (LGBTQ) youth were at higher risk of depression, suicidality, and tobacco, alcohol, and other drug use. These increased risks stem from elevated rates of rejection, discrimination, and victimization. During the pandemic, risks were further compounded by the loss of relationships in schools, clubs, or other community venues where LGBTQ youth found support and affirmation. Laura Erickson-Schroth, MD, a psychiatrist at the Hetrick-Martin Institute, a New York City-based LGBTQ youth organization, reported that youth members of the institute are looking for more frequent counseling sessions. According to her, there were at least one-third more requests for initial psychiatry visits during 2020 than during the same period in 2019.

Results from a study commissioned by New York City’s ACS found one-third of the city’s youth in foster care identifies as LGBTQ, an order of magnitude greater than the general population. Nearly three-quarters of these youth are Black, and one-third identify as Hispanic/Latino. LGBTQ youth are placed in group homes and other campus settings rather than foster families more often than their non-LGBTQ peers, and they are more likely to be dissatisfied with their placement. The study also found these youth experience a greater burden of depression.

According to Dylan Waguespack, director of public policy and external affairs of True Colors United (https://truecolorsunited.org/), 20% to 40% of homeless youth identify as LGBTQ. True Colors United is a national organization dedicated to ending LGBTQ youth homelessness. Although family conflict, involvement in the foster care system, and involvement in the criminal justice system are among the factors that contribute to homelessness among these youth, poverty is often the root cause. Not only are these youth at risk for adverse mental health outcomes because of rejection and discriminatory behaviors, they often face traumatic experiences through conflict with their families, involvement in overwhelmed and poorly informed state programs.

Agencies that previously made efforts to address racial, social, gender, or sexuality based inequities before the pandemic have become even more overwhelmed with the increase in housing and food insecurity, increased unemployment, instability in the agency’s own staff, and the need to rapidly implement physical distancing and other public health measures in routine work. Overwhelmed and encumbered agencies are increasingly unable to provide critical services for LGBTQ youth, leaving them powerless in impeding a downward spiral into homelessness and associated negative ramifications.

Even as the pandemic ends, there may be continual struggles and support needs. Fortunately, there are ways psychiatrists and other mental health care professions can help.

Some of these methods include the following:

- Financially donate or fund organizations that support or serve LGBTQ youth.
- Advocate for programs that decrease income inequality and promote housing and food security.
- Enable rapid interventions to prevent LGBTQ youth from entering the foster care and criminal justice systems.
- Use clinical, teaching, institutional, and forensic roles to speak out and advocate for this vulnerable group of young people.
- Share resources and references for supportive organizations with patients who are LGBTQ (Table).
Medical Liability Costs Are on the Rise

Todd Shryock

Medical liability insurance premiums are increasing after a decade of mostly steady rates, according to a new analysis from the American Medical Association (AMA). In 2020, more than 30% of premiums reported on a survey of liability insurers increased from the previous year, the highest percent increase since 2005.

For a second consecutive year there has been an exceptional surge in the size of the increase. Between 2010 and 2018, the share of premiums that increased ranged from 12% to 17%. In 2019, that proportion almost doubled to 26.5% and rose in 2020 to 31.1%.

According to the AMA analysis, although some 2020 premiums may have been set after the onset of the COVID-19 pandemic, it was still too early for them to be affected by it.

“Increases in medical liability premiums compound the economic stress on medical practices as the COVID-19 pandemic resulted in significant reductions to patient volume and revenue, and higher expenses for scarce medical supplies,” AMA President Susan R. Bailey, MD, said in a news release. “Practice revenue has not fully recovered as the pandemic has stretched on and a protracted upward trend in medical liability premiums will threaten the viability of many practices that already face a difficult road to recovery.”

The analysis identified the 14 states that had premium increases of 10% or more. Those states and their shares of reported premiums that increased by such magnitude in 2020 are: Kentucky (29.6%), South Carolina (27.8%), Maryland (18.8%), Nebraska (16.7%), Oregon (16.7%), Montana (16.7%), Georgia (14.8%), Missouri (14.8%), New Hampshire (13.3%), Illinois (11.9%), Michigan (11.6%), Texas (9.2%), North Carolina (6.7%), and Virginia (1.3%).

The AMA report also found striking differences in premiums by geography. “Keeping medical liability premium growth in-check is imperative to ensure patient access to care is not jeopardized by unaffordable liability insurance costs that make it impossible for physicians to remain in practice,” said Bailey. “This concern is particularly pressing given the negative impact that the COVID-19 pandemic has had on access and practice viability, as many physicians have had to suspend patient visits or elective procedures, and some have had to close their practices.”

Together with state medical societies, the AMA is pursuing both traditional and innovative medical liability reforms to preserve premium stability. This includes limited and targeted emergency protections for physicians who continue to treat patients during the pandemic without adequate resources and support.

The newly released AMA analysis on medical liability insurance premiums is based on an annual survey of professional liability insurers conducted by the Medical Liability Monitor (MLM). The MLM reports base premiums for 3 specialties in each state where the responding insurers provide coverage.

Concluding Thoughts

LGBTQ youth have long experienced marginalization and significantly increased risk of poor mental health outcomes. The COVID-19 pandemic sharpened the crisis and brought clarity to the precariousness of social service agencies that address those needs. Strengthening the support system for these youth and their allies and making agencies more inclusive of their voices is critical to help these young people achieve a healthy and fulfilling life.

Dr Adelson is the director of the Youth Equity Science/YES Project and senior visiting fellow at Yale Law School. He is also an assistant clinical professor at Columbia University and an adjunct clinical assistant professor at Cornell Weill Medical College. Dr Ahola is the medical director emeritus at Weill Cornell Center for Human Rights. Dr Barber is the past president and journal editor for the Association of LGBTQ Psychiatrists and is an MDIV candidate at Union Theological Seminary. Dr Casoy is a community and public psychiatrist in New York City. Dr Drescher is a clinical professor of psychiatry at Columbia University and an adjunct professor at New York University. He is also a distinguished life fellow of the American Psychological Association and the past president of the Group for Advancement of Psychiatry.

Dr Erickson-Schroth is an assistant professor of psychiatry at Columbia University Medical Center and a consulting psychiatrist at Hetrick-Martin Institute for LGBTQ youth.

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RESEARCH UPDATE

Which Pharmacotherapies Are Most Effective for Schizoaffective Disorder?

Brian Miller, MD, PhD, MPH

Schizoaffective disorder includes both psychotic and affective symptoms (Table 1), with separate bipolar and depressive subtypes. ICD-11 aims to improve diagnostic accuracy and differential diagnosis of schizoaffective disorder. There is debate whether schizoaffective disorder is a separate illness or is part of the continuum of schizophrenia and mood disorder spectrum. Pharmacotherapy recommendations for schizoaffective disorder are generally derived from studies on schizophrenia and bipolar disorder; thus, symptoms are most commonly treated with antipsychotics, mood stabilizers, and/or antidepressants. Only paliperidone has an indication specifically for schizoaffective disorder.

Cohorts Studied

To explore the efficacy of pharmacotherapies for schizoaffective disorder, Lintunen and colleagues looked at 2 nationwide cohorts. Treatments included oral and long-acting injectable (LAIs) antipsychotics, mood stabilizers, antidepressants, and benzodiazepines and nonbenzodiazepines together (zopiclone, zolpidem, and zaleplon, also known as Z-drugs). Lintunen et al analyzed 2 cohorts from nationwide Finnish and Swedish registers. The Finnish cohort included 7655 patients treated for schizoaffective disorder, based on inpatient care as recorded in the Finnish Hospital Discharge Register. The Swedish cohort included 7525 individuals aged 16 to 64 years with schizoaffective disorder who were identified based on inpatient care as recorded in the Swedish Hospital Discharge Register. The Swedish cohort included 7655 patients treated for schizoaffective disorder, based on inpatient care as recorded in the Finnish Hospital Discharge Register. The Swedish cohort included 7525 individuals aged 16 to 64 years with schizoaffective disorder who were identified based on inpatient care as recorded in the Finnish Hospital Discharge Register.

The main exposure was antipsychotics, based on Anatomical Therapeutic Chemical classification code N05A (except lithium); antidepressive medicine included mood stabilizers, antidepressants, and benzodiazepines and/or Z-drugs. Psychotropic medication use periods were based on the PRE2DUP method. The primary outcome measure was hospitalization due to psychosis. The authors also analyzed a composite measure of treatment failure, which included psychiatric hospitalization, change in medication, and death.

Analyses were conducted in each cohort separately using within-individual design and Cox regression models (hazard ratios [HRs] and 95% CIs), with P values adjusted for multiple comparisons. For antipsychotic effectiveness, the reference was antipsychotic nonuse. Nonantipsychotic medications were considered as adjunctive therapies, with antipsychotic use without adjunctive use as the reference (eg, olanzapine monotherapy was the reference for comparisons with olanzapine-mood stabilizer analyses). Data on 16 most commonly used antipsychotics were reported. Five oral antipsychotics (clozapine, olanzapine, quetiapine, risperidone, and aripiprazole) and LAIs (as a single category) were analyzed in combinations with adjunctive pharmacotherapies.

The Outcomes

In both cohorts, 60% of the study subjects were female. Mean age was 45 to 47 years. During follow-up, 13% of the Finnish cohort and 22% of the Swedish cohort were censored because of a change in diagnosis to schizophrenia. The median follow-up was 8 years in the Swedish cohort and 11 years in the Finnish cohort. During the follow-up, about half of the participants had a hospitalization for psychosis. Approximately 90% of individuals used antipsychotics during the follow-up; first-generation agents were more common in Sweden, and clozapine and antipsychotic polypharmacy were more common in Finland. About half of the patients had concurrent antipsychotic and antidepressant use, whereas mood stabilizers were used in 41% of the Swedish and 47% of the Finnish cohort. Benzodiazepines/Z-drugs were used in 72% of the Swedish and 61% of the Finnish cohort.

In both groups, use of clozapine (HR, 0.49-0.50), LAIs, and polypharmacy (HR, 0.51-0.57) were consistently associated with a decreased risk of inpatient hospitalization versus antipsychotic nonuse (Table 2). Notably, quetiapine use was not associated with a decreased risk of psychosis hospitalization in either country. In sensitivity analyses, the pattern of findings was similar.

Antipsychotics plus mood stabilizers were associated with a 16% to 24% decreased risk of a psychosis hospitalization (HR, 0.76-0.84). Antidepressant use was associated with a 10% decreased risk of inpatient hospitalization in the Swedish cohort (HR, 0.90), but not in the Finnish cohort (HR, 1.00). By contrast, Z-drug use was associated with a 7% to 21% increased risk of hospitalization, even after censoring the first 30 days of use. The overall pattern of findings remained similar with the broader outcome of any psychiatric hospitalization (instead of hospitalization for psychosis).

The authors found that exposure to antipsychotics was associated with a decreased risk for inpatient hospitalization in patients with schizoaffective disorder. Furthermore, the combination of antipsychotics and adjunctive mood stabilizers (versus antipsychotic monotherapy) was also associated with lower risk of psychosis hospitalization. The evidence was much less robust for adjunctive antidepressants. Adjunctive use of benzodiazepines/Z-drugs was associated with an increased risk of hospitalization.
Tips for Lithium Dosing for Optimal Renal Safety

David N. Osser, MD

To minimize renal side effects, lithium is best administered once daily at night, and one should routinely use the regular-release (24-hour half-life) preparation. It comes in tablets or capsules. Capsules are sometimes better tolerated because they do not have the salty taste that can contribute to nausea. They also are available in 150-mg doses, which is a convenient size for some patients on doses like 450 or 750 mg daily. Plasma levels during acute treatment should not be allowed to go higher than 1.0 mEq/L for a lower risk of long-term kidney harm.

The regular-release formulation is preferred over the sustained release version (Lithobid; now available as a generic) because it provides superior pharmacokinetics for sparing the kidneys of potential harm. Studies have shown that once-a-day lithium at night, compared with multiple daily doses, lowers urinary volume and other symptoms of the lithium-induced dia-betes insipidus-like syndrome.1 After the patient reaches the 12-hour postdose level following their evening dose (eg, 0.7 mEq/L), the patient’s level continues to drop during the day, reaching a low point just before the next once-daily dose. This low level is thought to give the kidneys an opportunity to have relatively little lithium coursing through them, which aids recovery from dys-function, such as increased urine volume. When using a longer-acting preparation, further lowering the level during the second half of the day is minimal and, hence, the protective effect should be lower.

Trials examining renal biopsy results also found that multiple daily doses were associated with more pathologic changes to the kidneys.2 Why doesn’t the higher peak lithium level associated with a long once-daily dose harm the kidneys? We can only say, based on the studies, that this effect must be less harmful than the absence of the daily low trough level. No reduction in effectiveness has been noted in any of the trials of once-daily lithium.

Another possible advantage of giving the whole dose at night is that the kidneys filter lithium more slowly at night. The net effect is that you only need 80% of the daily divided doses when changing patients to a once-nightly regimen. For instance, if someone was on 1500 mg daily in divided doses, they would usually need 1200 mg at night to get the same 12-hour postdose level. The once-daily dose at night reduces the total exposure and need to excrete lithium as compared with the divided doses. It is also possible that tremors will be less bothersome with the once-daily dose: the worst of the tremors will occur in the middle of the night when the patient is (hopefully) sleeping, and the lowest level of severity will be in late afternoon and evening.

The optimal level for maintenance treatment with lithium is 0.6 mEq/L to 0.8 mEq/L, according to a recent analysis of the pertinent evidence.4 Higher maintenance levels are associated with a greater risk of long-term kidney harm and (surprisingly) more frequent depressive episodes.5 If patients are having breakthrough manias or hypomanias despite optimal maintenance levels of lithium and are also prone to serious depressions, it is better to add another antimanic agent instead of increasing lithium. Most patients with bipolar disorder experience more time in depressive states than manic states, so this will be a very common situation. If there are breakthrough depressions, consider adding lamotrigine, lurasidone, quetiapine, or cariprazine.6

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Different Strokes: How to Spot and Treat Poststroke Depression

Rajesh R. Tampi, MD, MS, DFAPA, DFAAGP; and Estee George, PhD

It is estimated that in the United States alone, approximately 795,000 individuals have a stroke annually. The prevalence of stroke is greater among men than women, but the stroke incidence doubles among postmenopausal women. Furthermore, stroke was rated as the third most common cause of disability adjusted life-years worldwide in 2010. In the United States, stroke has been established as the most burdensome of all neurological disorders. One study found that among the long-term (15 year) survivors of stroke, 33.8% have mild disability, 14.3% have moderate disability, and 15.0% have severe disability (Figure 1). The prevalence of disability increased with time, but 10% of these individuals had lived with moderate-severe disability since their stroke.

Available evidence indicates that there are a multitude of neuropsychiatric syndromes that occur after a stroke (Figure 2). Poststroke bipolar disorder, mania, and psychotic symptoms are rare sequelae to stroke. Cognitive impairment occurs in approximately one-third of individuals post stroke. These neuropsychiatric manifestations often impede the recovery of motor functioning, reduce social functioning, and decrease the overall quality of life.

Epidemiology

A recent meta-analysis found that the prevalence of any depressive disorder post stroke is approximately 33.5%. In this study, the point prevalence of major depression was 17.7% with the prevalence for minor depression being 13.1%. Prevalence of dysthymia and adjustment disorder was 3.1% and 6.9%, respectively. An earlier meta-analysis found that the frequency of poststroke depression was approximately 31%. The proportion of those with depression between 1 and 5 years after stroke was 25%, and the proportion of those with depression at 5 years after stroke was 23%.

In the DSM-5, poststroke depression (PSD) is classified under the criteria for “Depressive Disorder Due to Another Medical Condition” (Figure 3). To meet the DSM-5 criteria, individuals should present with a prominent and persistent period of depressed mood or markedly diminished interest or pleasure in all or almost all activities. The history, physical examination, or laboratory findings should show that the depressive symptoms are due to the direct pathophysiological consequence of a stroke. Furthermore, the presence of depressive symptoms should not be better explained by another mental disorder, including an adjustment disorder, nor should the depressive symptoms occur exclusively during the course of a delirium. In addition, these symptoms should cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

PSD symptoms can be further subclassified as...
presenting with (1) depressive features when all criteria for a major depressive episode are not meet, (2) a major depressive-like episode when the criteria for a major depressive episode are met, and (3) mixed features when symptoms of mania or hypomania are also present but do not predominate in the clinical presentation.

PSD phenomenology is similar to, but not the same as, that described by other individuals with depression.8 For example, individuals with PSD are less likely to report “inability to feel” or “disturbed sleep.” In addition, individuals with PSD may be less likely to report anhedonia and apathy when compared with other individuals who have depression. In one study, researchers compared symptoms in (1) poststroke patients with and without depression, (2) individuals who were being seen in general practice, and (3) patients with symptomatic atherosclerotic diseases.10 They found that although the 3 cohorts demonstrated broadly similar symptom profiles, as well as comparable levels of individual symptom prevalence, the individuals with PSD had more severe symptoms than individuals in the other 2 groups.

A recent meta-analysis by Shi et al indicated that a history of mental illness (depression/anxiety) was the highest-ranking risk factor for PSD (odds ratio [OR] 2.93).11 Other risk factors for PSD were family history of mental illness (OR=1.95), age (<70 years, OR=1.94), female sex (OR=1.77), level of handicap (OR=1.52), severity of stroke (OR=1.12), and neuroticism (OR=1.08). The investigators also found that education (>8 years) and social support (OR=0.93) were protective factors for PSD. Brain damage in the left frontal lobe and left basal ganglia was associated with PSD, and specified levels (<10.2 mg/ml) of brain-derived neurotrophic factor and leptin (>20.7 mg/ml) were risk factors for PSD. Biochemical factors, including interleukin-1b (IL-1b) and intercellular cell adhesion molecule-1 (ICAM-1), hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, and myocardial infarction were not found to be associated with PSD.

Consequences
In a prospective observational study of individuals who were post stroke and in the emergency department or admitted to acute care in designated stroke centers, individuals with PSD had more severe strokes, greater functional handicap, and longer hospital stays and were less likely to be discharged home following acute hospitalization (all P < .001) than patients without PSD.13 One systematic review indicated that individuals with PSD tend to experience a moderate increase in the risk of poor functional outcome (OR = 2.16) when compared with stroke patients without depression.12 This association did not seem to be caused by poor reha-

bilitation and functional improvement among individuals with PSD.

Suicidal ideation is also a consequence of PSD. A meta-analysis by Bartoli et al found the pooled proportion of suicidal ideation among stroke survivors was 11.8%.14 Current (OR=11.50; P < .001) and past (OR=6.96; P < .001) depression, recurrent stroke (OR = 1.77; P < .001), disability (P = .01), and cognitive impairment (P = .03) were all associated with suicidal ideation. Suicidal ideation was less likely to occur in stroke survivors who were married (OR = 0.63; P < .001), employed (OR = 0.57; P = .02), and had higher education levels (OR=0.55; P=.002). A meta-analysis by Cai et al found that PSD was associated with significantly increased risk for mortality among stroke survivors (HR = 1.59).15

Pathogenesis
The pathogenesis of PSD involves complex interactions between neuroanatomical and neurochemical factors.16 It is thought that the processes involved in development of PSD include reduced levels of monoamines, abnormal neurotrophic response to the occurrence of stroke, increased inflammation in the brain, dysregulation of hypothalamic-pituitary-adrenal (HPA) axis, and glutamate-mediated excitotoxicity.17,18 Available studies indicate that large lesions in critical areas of the brain, including the left frontal lobe and basal ganglia or the accumulation of silent cerebrovascular lesions beyond a critical threshold, may intercept the pathways of monoamine neurotransmitters or pathways that control mood regulation.19 Cytokines that are produced post stroke increase glutamate-induced excitotoxicity, resulting in neuronal death in critical areas of the brain. This may also lead to the enlargement of cerebral infarctions. This process, coupled with hypercortisolism induced by stress or inflammation after the stroke, may reduce intracellular serotonin transporters, resulting in depression. Additionally, hippocampal neurogenesis may be inhibited by the interaction among cytokines, glucocorticoid, and neurotransphin. Available evidence indicates that these neurobiological processes, seen among individuals who develop PSD, may differ from individuals who do not develop depression after a stroke, but the details regarding these complex mechanisms are only emerging.17,18

Assessment
Although fairly common, PSD is often underdiagnosed.19 Differential diagnosis is difficult, as many of these individuals who are post stroke may present with cognitive impairment and may not be able to report their symptoms accurately (Table). In addition, some symptoms of stroke and depression (eg, loss of appetite, difficulty concentrating, and sleep disorders) may be indistinguishable from one another. In these situations, the presence of nonsomatic symptoms including guilt, depressed mood, hopelessness, or worthlessness is more suggestive of PSD.20

In one study, PSD was diagnosed in only 4.8% of the patients, and only 6.7% of these individuals were treated with a new antidepressant. However, compared with patients admitted to standard units, individuals admitted to specialized stroke units were more likely to be diagnosed with depression (5.2% vs 4.0%; P < .014) and were more likely to receive a new prescription for an antidepressant (7.8% vs 4.5%; P < .001). These results indicate that there should be routine screening post stroke for PSD. Additionally, specialized stroke unit care may improve the detection and treatment of PSD.

A number of tools may be helpful in identifying PSD. One meta-analysis found that the Center of Epidemiological Studies-Depression Scale (CES-D) (sensitivity, 0.75 and specificity, 0.88), the Hamilton Depression Rating Scale (HDRS) (sensitivity, 0.84 and specificity, 0.83), and the Patient Health Questionnaire (PHQ)-9 (sensitivity, 0.86 and specificity, 0.79) were optimal screening tools.22 The PHQ-2 performed less well than other measures. However, the investigators found that the clinical utility of these tools was modest for case-finding. They cautioned that these screening tools should not be used in isolation; a more detailed clinical assessment to detect PSD should also be used.

Prevention
A meta-analysis by Hackett et al evaluated interventions for preventing PSD. The investigators included data from 10 pharmaceutical trials (12 comparisons) and 4 psychotherapy trials.23 Most of the participants were recruited within 1 month of acute stroke, and the duration of treatment ranged from 2 weeks to 1 year. The proportion of participants meeting the study criteria for depression was lower in the antidepressant-treated group; however, meta-analysis was not performed, as the study methods and end point measures varied among studies. There was no evidence of benefit of antidepressants on the mean depression scores at the end of treatment or change in mean scores from baseline. Additionally, there was no evidence of pharmacotherapy improving cognitive function or activities of daily living (ADL) or reducing disability. There was no clear evidence of harm demonstrated in the analysis of adverse events. The investigators noted benefit of
In a meta-analysis that included data from 10 randomized placebo-controlled trials (RCTs) that evaluated the prophylactic effects of antidepressants in nondepressed individuals with stroke to prevent PSD, Chen et al found the pooled occurrence rates of newly developed PSD cases in the intervention and control groups were 12.54% (41 of 327 participants) and 29.17% (91 of 312 participants), respectively. Both selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) were associated with reductions in the incidence of PSD. The reductions in the incidence of PSD were not related to the interval between stroke onset and the administration of an antidepressant (P = .47), and the prophylactic effects of antidepressants were not related to duration of their use (P = .11).

In a recent meta-analysis, Gu et al included data from 12 studies that evaluated the use of prophylactic antidepressants to prevent the occurrence of PSD. The investigators found antidepressants following acute stroke reduced PSD incidence (relative risk [RR] = 0.33, P < .001). There were no differences detected in efficacy noted between the SSRIs, TCAs, and serotonin norepinephrine reuptake inhibitors (SNRIs) in the subgroup analysis. When compared with the control group, the RR of PSD recurrence during the follow-up period in the treatment group was 0.51 (P < .001). The pooled mean difference in reduction of depression severity on the HDRS between the antidepressant and control groups was 5.73 (P < .001). Additionally, there were no differences detected in efficacy noted between the SSRI, TCA, and SNRI antidepressants. In a second network meta-analysis, the investigators included data from 15 RCTs in which 13 antidepressant drugs were considered. The investigators found that for efficacy, paroxetine was ranked the best antidepressant for reduction in depression scores at the end of treatment, followed by imipramine, reboxetine, nortriptyline, citalopram, and fluoxetine. They also found that duloxetine ranked the best for the reduction in depression scores at durations of 4 weeks and 8 weeks. For tolerability, paroxetine was ranked the best, but there was no significant difference noted between any of the comparisons. In a third network meta-analysis of 14 RCTs with 9 different antidepressant treatments, the investigators found that doxepin, paroxetine, and nortriptyline were significantly more effective than placebo (standardized mean differences: -1.93, -1.39, and -1.25, respectively) in the treatment of PSD.

In a study that evaluated transcranial direct current stimulation (tDCS) for PSD, the investigators randomized 48 antidepressant-free individuals with PSD into 2 groups: active and sham tDCS. Participants received twelve 30-minute sessions of left/cathodal right dorsolateral prefrontal tDCS over a 6-week period: once daily on weekdays for 2 weeks, then 1 session every other week. The primary outcome was a change in the 17-item HDRS at 6 weeks. The investigators found that active tDCS was superior to sham at the end point (P < .001). The response and remission rates were also significantly higher in the active treatment group (37.5% and 20.8%, respectively) when compared with the sham treatment group (4.1% and 0%, respectively). The number-needed-to-treat for response and remission were 3 and 5, respectively. There were no changes in cognitive performance due to tDCS, and the frequency of adverse events was not significantly different between the active and sham groups at all time points. Additionally, no serious adverse events were reported. The investigators did not identify any potential predictors of response including headache onset after stroke, duration of the depressive episode, and duration of the stroke episode.

A systematic review and meta-analysis of 22 RCTs evaluated the effect of repetitive transcranial magnetic stimulation (rTMS) on PSD. The primary outcome was severity of depression as measured by the HDRS. The secondary outcomes were response rates, remission rates, stroke severity, and ability to perform daily activities. The investigators found that TMS was beneficial for PSD on all of the following: HDRS (P < .001); response rates (OR = 3.46; P < .0001); remission rates (OR = 0.89; P < .0001); National Institutes of Health Stroke Scale (P < .001); ADL (P < .001); and Montgomery-Asberg Depression Scale (P = .0001). A total of 15 (1.7%) participants in the active treatment group and 6 (0.7%) participants in the control group experienced headache; 2 (0.2%) participants in the active treatment group and 9 (1.0%) participants in the control group developed gastrointestinal reactions; 3 (0.3%) participants in the active treatment group and 7 (0.8%) participants in the control group had dry mouth; 1 (0.1%) participant in the active treatment group suffered from tinnitus; 1 (0.1%) participant in the active treatment group felt weak; and 6 (0.7%) participants in the control group experienced other adverse events. The investigators did not find any statistically significant differences in withdrawals due to adverse events between the 2 groups; 0.2% (2 of 881) of patients in the control group withdrew due to gastrointestinal effects. Because of the significant heterogeneity between the different studies, the effect of frequency of treatment, site,
duration of illness, type of basic treatment, type of control intervention, and total session on outcomes could not be evaluated.

Concluding Thoughts

PSD is a common sequela of stroke. The pathogenesis of PSD involves complex interactions between both neuroanatomical and neurochemical factors. PSD is associated with more severe strokes, greater functional handicap, longer hospital stays, lower likelihood of discharge to home following acute hospitalization, and a greater risk for common risk factors for PSD include a history of mental illness (depression/anxiety), a family history of mental illness, age (<70 years), female sex, level of handicap, severity of stroke, and neuroticism.

Although fairly common, PSD often remains underrecognized and poorly treated. Available evidence indicates efficacy of both nonpharmacological and pharmacological treatment strategies for the prevention of PSD. Early identification and appropriate management of PSD will reduce the morbidity and mortality due to this condition. Future research should investigate the pathophysiological underpinnings of PSD, so that more effective preventative and treatment strategies can be developed.

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Consultation-Liaison Psychiatrist

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The University of Miami (UM) Miller School of Medicine is an academic medical center with extensive clinical facilities including the NCI-designated Sylvester Comprehensive Cancer Center (Sylvester). All Sylvester physicians are on the faculty of the Miller School of Medicine, South Florida’s only academic medical center.

CV’s and letter of interest can be directed to Maria Rueda-Lara, M.D. email: mrueda2@med.miami.edu

Psychiatrist retiring from an established practice of over 30 years. Adult and Geriatric patients. Two hospitals in the area to serve patients. On the beautiful West Coast of Florida an hour drive north of Tampa. Gorgeous natural setting with a host of outdoor activities.

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**PSYCHIATRY**

& Psycho-Oncology

The Department of Psychiatry and Behavioral Sciences at the University of Miami and the NCI-designated Sylvester Comprehensive Cancer Center announce a search for an academic psychiatrist with interest and experience in Consultation Liaison Psychiatry. Applicants will work collaboratively with fellow psycho-oncology providers including psychologists, psychiatrists, oncology social workers and other multidisciplinary members providing oncology services.

**JOB DESCRIPTION**

The candidate will provide psychiatric consultation-liaison services across inpatient and outpatient oncology settings.

As a faculty member of the Department of Psychiatry and Behavioral Sciences, the candidate will be expected to participate in psycho-oncology teaching and training activities.

Research opportunities in psycho-oncology are also available.

**QUALIFICATIONS OF THE PSYCHIATRIST**

- Board certification in Psychiatry.
- Board eligibility/certification in C-L Psychiatry would be preferred but experience will be considered.
- Demonstrated record of interest or training in psycho-oncology preferred.

**COMPENSATION & BENEFITS**

This dynamic position commands an outstanding salary enhanced by an attractive benefits package, including but not limited to:

- Competitive compensation including bonus programs and vacation.
- Comprehensive benefits include health/dental/vision, paid malpractice, and 403(b) plans.

The University of Miami (UM) Miller School of Medicine is an academic medical center with extensive clinical facilities including the NCI-designated Sylvester Comprehensive Cancer Center (Sylvester). All Sylvester physicians are on the faculty of the Miller School of Medicine, South Florida’s only academic medical center. Structured clinical teaching as well as didactic based therapeutic procedures. There is no required on-call, no evenings, no weekends, no nights, or no holidays, although physicians can sign up for voluntary night and weekend shifts at additional pay. Attending Psychiatrists are eligible for a faculty appointment at Tufts at appropriate rank, a competitive salary and excellent benefits.

**INTERESTED CANDIDATES**

Please send your confidential CV to: Jennifer Colon

Physician Recruiter
Tufts Medical Center Physicians Organization
800 Washington Street, #1013
Boston, MA 02111
Fax: 617-636-7523
Email: jcolon@tuftsmedicalcenter.org

**www.tuftsmedicalcenter.org**

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**COMPASS HEALTH INC., D/B/A PATHWAYS COMMUNITY HEALTH IN INC.**

MISSOURI

**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@phhc.org Fax: 417-532-6606.

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**PSYCHIATRIST**

Tufts Medical Center is hiring a Staff Psychiatrist at Tewksbury Hospital, Hathorne Units, located 20 miles North of Boston. Tewksbury Hospital provides therapeutic environment to provide patient focused medical and psychiatric care and diagnostic services meet the needs of patients with complex chronic psychological or social needs. Tewksbury Hospital is in the process of becoming the model facility for providing recovery oriented, trauma informed, family focused, person centered and strength based clinical and rehabilitative treatment. Board Certification or Board Eligibility is required.

Create a great start to your career with a position that provides a healthy work life balance and a supportive team environment. The position has no required on call, no weekends, no evenings and no holiday commitments. In this position you will develop your interest in inpatient, consultation liaison, and forensic psychiatry skills to best serve the diverse needs of our patients. Applicants should be familiar with evidence based therapeutic procedures. Night and weekend shifts may be picked up to be generously remunerated above base salary if desired. This position has the support in place for a new residency graduates to be successful.

As a member of the Tufts Medical Center staff, you will also be eligible for faculty appointment, at a rank determined by the Tufts University School of Medicine.

Faculty Members are expected to demonstrate excellence in one or more Areas of Distinction that provide a unifying theme for their Academic Activities, achievements and scholarship; to demonstrate effectiveness in Educational Activities; and to participate in Academic Service; along with participation in the education mission which may include clinical teaching as well as didactic instruction for medical students, residents and other learners.

**INTERESTED CANDIDATES**

Please send your confidential CV to:

Jennifer Colon
Physician Recruiter
Tufts Medical Center Physicians Organization
800 Washington Street, #1013
Boston, MA 02111
Fax: 617-636-7523
Email: jcolon@tuftsmedicalcenter.org

**www.tuftsmedicalcenter.org**

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**ADDICTION PSYCHIATRIST ADVERTISEMENT**

Tufts Medical Center is hiring a full-time board-certified psychiatrist or Psychiatric Nurse Practitioner who is interested in becoming the leader of a multidisciplinary treatment team at The Solomon Carter Fuller Mental Health Center, a Massachusetts DMH teaching hospital located in Boston. The successful candidate must have a current and valid MA license and unrestricted DEA and MA Controlled Substance Registration. Possess a minimum of three years of post-residency experience, experience in working with inpatients in a consultation liaison capacity, and interest and experience in working with forensic patients and patients with both serious mental illness and substance use disorders.

The Solomon Carter Fuller Mental Health Center is a model facility that provides trauma-informed, recovery-oriented, person-centered and strength-based clinical and rehabilitative treatment. Applicants should be familiar with these evidence-based therapeutic procedures. There is no required on-call, no evenings, no weekends, no nights, or no holidays, although physicians can sign up for voluntary night and weekend shifts at additional pay. Attending Psychiatrists are eligible for a faculty appointment at Tufts at appropriate rank, a competitive salary and excellent benefits.

**INTERESTED CANDIDATES**

Please send your confidential CV to:

Jennifer Colón
Physician Recruiter
Tufts Medical Center Physicians Organization
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Boston, MA 02111
Fax: 617-636-7523
Email: jcolon@tuftsmedicalcenter.org

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**TUFFS MEDICAL CENTER**

Addiction Psychiatrist Advertisement

Tufts Medical Center is through its department of psychiatry at the Tufts School of Medicine and is seeking an experienced leader in addiction psychiatry to serve as the Director of Addiction Psychiatry at Tufts Medical Center and to begin the development of an academically and clinical program at Tufts Medical Center.

Qualified candidates will be eligible for a full time faculty position at Tufts University School of Medicine at the appropriate academic rank. The Director of this service will interface closely with the Chief of Consultation-Liaison Psychiatry, leadership of medical, surgical and ED services, training leadership across the medical center and the Chief Medical Officer.

**QUALIFICATIONS**

- M.D. or D.O. BC/BE in Psychiatry and formal subspecialty training in Addiction Psychiatry, BC/BE in addiction psychiatry.
- Preference will be given to those with experience in academic medical center addiction and consultation settings
- Possess credentials for a faculty appointment at the minimum rank of Assistant Professor
- Medical licensure in the Commonwealth of Massachusetts.
- Tufts Medical Center and Tufts Medical Center Physicians Organization are EEOC employers and candidates from minority and underrepresented groups are strongly encouraged to apply.

Tufts Medical Center is an exceptional, not-for-profit, Level 1 Trauma, 415-bed academic medical center that is home to both a full-service hospital for adults and the Floating Hospital for Children. Conveniently located in downtown Boston and embedded within the Tufts University Health Sciences campus, the Medical Center is the principal teaching hospital for the Tufts University School of Medicine. Floating Hospital for Children is the full-service children’s hospital of Tufts Medical Center and the principal pediatric teaching hospital of Tufts University School of Medicine. Division Faculty members are actively supported in pursuing the outstanding opportunities for collaborative academic work that span the academic spectrum across the campus.

We offer competitive compensation, comprehensive benefits package, and a generous employer retirement plan contributions.

**INTERESTED CANDIDATES**

Please send your confidential CV to:

Jennifer Colón
Physician Recruiter
Tufts Medical Center Physicians Organization
800 Washington Street, #1013

**BOSTON, MA 02111**

**Telephone:** 857-275-6126

**Fax:** 617-636-6366

**Email:** jcolon1@tuftsmedicalcenter.org

**www.tuftsmedicalcenter.org**

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Tufts Medical Center is an exceptional, not-for-profit, Level 1 Trauma, 415-bed academic medical center that is home to both a full-service hospital for adults and the floating hospital for children. Conveniently located in downtown Boston and embedded within the Tufts University Health Sciences campus, the Medical Center is the principal teaching hospital for the Tufts University School of Medicine. Floating Hospital for Children is the full-service children’s hospital of Tufts Medical Center and the principal pediatric teaching hospital of Tufts University School of Medicine. Division Faculty members are actively supported in pursuing the outstanding opportunities for collaborative academic work that span the academic spectrum across the campus.

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SOUTH CAROLINA

Inspire health. Serve with compassion.
Be the difference.

Seeking Candidates for Director of Adult Residency Training Program in Psychiatry
Greer, SC

Prisma Health, the largest not-for-profit healthcare provider in South Carolina, currently seeks board certified psychiatrist to join our growing department and training program. We are seeking qualified candidate for program director for our adult residency training program in Greer, South Carolina. Ideal candidates will be appointed to the University of South Carolina School of Medicine Greenville faculty and work closely with the department chair as we welcome our second class of eight residents in July 2021.

Details Include:
- Candidate must be board certified in psychiatry and demonstrated accomplishments as an educator with leadership experience in academic psychiatry for a minimum of 3 years.
- Must possess or be eligible or license in the state of South Carolina.
- Experience in an outpatient mental health setting, including telepsychiatry services
- Clinical responsibilities in the outpatient setting and consultation-liaison coverage in small hospital
- Academic faculty position working with residents and medical students
- Rich benefits package including relocation, malpractice, health and dental insurance
- CME allowance and competitive compensation
- Responsibilities:
  - Direct teaching and training
  - Evaluating and supervising residents
  - Mentoring
  - Developing, monitoring, and evaluating didactic courses and rotations
  - Facilitating required committees
  - Residency Education Committee, Clinical Competency, Program Evaluation Committee
  - Overseizing and organizing program accreditation processes

Prisma Health is a not-for-profit health company and the largest healthcare system in South Carolina. With nearly 30,000 team members, 18 acute and specialty hospitals, 2,947 beds and more than 300 outpatient sites with nearly 2,000 physicians, Prisma Health serves more than 1.2 million unique patients annually in its 21-county market area that covers 50% of South Carolina. Prisma Health’s goal is to improve the health of all South Carolinians by enhancing clinical quality, the patient experience and access to affordable care, as well as conducting clinical research and training the next generation of medical professionals.

Greer is located near Greenville, South Carolina and a beautiful place to live and work and the Prisma Health - Upstate catchment area is 1.3 million people. Greenville is located on the I-85 corridor between Atlanta and Charlotte, and is one of the fastest growing areas in the country. Ideally situated near beautiful mountains, lakes and beaches, we enjoy a diverse and thriving economy, excellent quality of life and wonderful cultural and educational opportunities.

*Public Service Loan Forgiveness (PSLF) Program Qualified Employer*

Qualified candidates should submit a letter of interest and CV to: Lexy Mason, Physician Recruiter, Lexy.Mason@prismahealth.org

Prisma Health is an equal opportunity employer which proudly values diversity. Candidates of all backgrounds are encouraged to apply.

TEXAS

West of Austin, TX - beautiful office
BC/BE Psychiatrist/Partner Needed for Psychiatric Private Practice

Hours: Monday - Thursday 9 - 5 pm

Patients pay at time of appointment - no insurances accepted. No electronic records;
Prescriptions are electronic. Share overhead costs. Call on every 5th weekend, usually no calls
31 years in practice - many new referrals every day!

Contact: David Flume at davidflume2@gmail.com

WASHINGTON DC

Department of Behavioral Health, Washington DC seeks
Supervisory Medical Officer (Psychiatry)

salary range $213,260 - $288,528 Per Annum

Department of Behavioral Health (DBH) seeks an experienced physician leader to serve as the Chief Clinical Officer. Provides overall leadership and direction of psychiatric and addiction medical support services. Coordinates and develop plans, policies, and procedures for administration of the behavioral health and general medical health care of persons in care. Adheres to legal and ethical practices and certification requirements. Establish quality of care and medical necessity criteria for the delivery of integrated behavioral healthcare services. Collaborates with senior level staff, community providers, and healthcare entities for development and review of initiatives, functions, and operation processes for consumers’ treatment and outcomes. Develop and monitor standards of care based upon best practices, state of the art models, and regulatory standards. Prepare testimony for oversight hearings, responds to formal inquiries and complaints, and serves as a subject matter expert in answering questions regarding expenditures and psychiatric needs. Provides clinical supervision to supervisor. Experience in providing leadership and clinical oversight for physicians, nurses, pharmacological and direct clinical care functions and specialty services medical officers and other staff members.

QUALIFICATIONS REQUIREMENT:
Applicants must meet the following requirements:
1. Graduation with a degree of Doctor of Medicine from the United States Medical School listed as approved by the Council of Medical Education of Hospitals American Association in the list published for the year of the applicant’s graduation;
2. A current, permanent, and full unrestricted District of Columbia license to practice medicine;
3. Completion of an approved full, rotating or mixed internship;
4. Completion of an approved residency program;
5. Certification in Psychiatry by the American Board of Psychiatry and Neurology or its equivalent; and
6. In addition to meeting the basic requirements, this position requires one (1) year of experience equivalent to the next lower grade level.

LICENSE REQUIREMENT:
A current, permanent, and full unrestricted District of Columbia license to practice medicine and Certification in Psychiatry by the American Board of Psychiatry and Neurology or its equivalent

EDUCATION:
Board Eligible or Certified in Psychiatry with a degree of Doctor of Medicine from the United States Medical School listed as approved by the Council of Medical Education of Hospitals American Association in the list published for the year of the applicant’s graduation.

Duration of Appointment:
MANAGEMENT SUPERVISORY SERVICE (AT WILL)
To Apply:
1. Pull up the website at www.dchd.dc.gov
2. Click on careers
3. Click on careers dc
4. Click on view all job
5. On the left hand side you can check on the a specific agency to see just that agency’s open positions
6. Click on Department of Behavioral Health under the Agency Heading *To Bring up the current announcements for DBH Only*
7. Once you have clicked on the Job Title the announcement will open up, click on Green “Apply for Job” #12036.
Online Resources at PsychiatricTimes.com have a new look!

As you enjoy the print edition of *Psychiatric Times™*, take a minute to go to our updated website for in-depth coverage and timely news and information.

Updated features include:

- Simple and flexible interface
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- Because delayed-release duloxetine capsules are not able to be crushed, opened, or sprinkled, Drizalma Sprinkle™ provides the first and only once-daily, delayed-release dosing option for patients who cannot or will not swallow solid medication forms.¹,⁵,⁶
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The duloxetine your patients require—approved in a sprinkle formulation designed for those who cannot or will not swallow solid forms of medication¹

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- Drizalma Sprinkle™ is available in 4 dosage strengths—20 mg, 30 mg, 40 mg, and 60 mg—for flexibility and easy titration¹
- Drizalma Sprinkle™ can be administered with or without food. Capsules can be opened, and the contents sprinkled over applesauce¹

IMPORTANT SAFETY INFORMATION (cont’d)

ADVERSE REACTIONS
The most common adverse reactions (≥5% and at least twice the incidence of placebo patients) were nausea, dry mouth, somnolence, constipation, decreased appetite, and hyperhidrosis.

DOSSING AND ADMINISTRATION
Drizalma Sprinkle™ may be taken with or without food. Drizalma Sprinkle™ may be swallowed whole [do not crush or chew capsule]; opened and sprinkled over applesauce; or administered via nasogastric tube.

DRUG INTERACTIONS
- Avoid concomitant use with potent CYP1A2 inhibitors
- Consider dose reduction with concomitant use with CYP2D6 substrates

USE IN SPECIFIC POPULATIONS
- Hepatic Impairment: Avoid use in patients with mild, moderate, or severe hepatic impairment
- Renal Impairment: Avoid use in patients with severe renal impairment
- Pregnancy: Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during treatment with Drizalma Sprinkle™. Third trimester use may increase risk of symptoms of poor adaptation (respiratory distress, temperature instability, feeding difficulty, hypotonia, tremor, irritability) in the neonate. Advise patients that Drizalma Sprinkle™ use during the month before delivery may lead to an increased risk for postpartum hemorrhage and may increase the risk of neonatal complications requiring prolonged hospitalization, respiratory support and tube feeding

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Drizalma Sprinkle™ provides effective therapy in one formulation for 4 different indications:

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- Chronic musculoskeletal pain in adults

IMPORTANT SAFETY INFORMATION (cont’d)

USE IN SPECIFIC POPULATIONS (cont’d)

- Lactation: Advise breastfeeding women using duloxetine to monitor infants for sedation, poor feeding and poor weight gain and to seek medical care if they notice these signs

To report SUSPECTED ADVERSE REACTIONS, contact Sun Pharmaceutical Industries, Inc. at 1-800-818-4555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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