On the front cover of the 2020 March issue, Psychiatric Times™ featured the story, “The New Game of Microbiology Clue: The Who, When, Where, & Why of the Novel Coronavirus.” When Nidal Moukaddam, MD, and Asim Shah, MD, began writing the story in January 2020, most of the public (and even much of the health care industry) knew very little of the virus that was devastating Wuhan and other parts of China. It seemed worlds away from our safe haven in the United States. By the time the issue arrived in our mailboxes, the country was on lockdown thanks to the coronavirus disease 2019 (COVID-19).

CONTINUED ON PAGE 13
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.

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.
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 attacks), including fatalities, were reported at a higher incidence in elderly patients with dementia-related psychosis taking risperidone, aripiprazole, and olanzapine compared to placebo. No studies have been conducted with oral paliperidone, INVEGA SUSTENNA®, or the 3-month paliperidone palmitate extended-release injectable suspension in elderly patients with dementia. These medicines are not approved for the treatment of patients with dementia-related psychosis.

Neuropsychiatric Malignant Syndrome (NMS): NMS, a potentially fatal symptom complex, has been reported with the use of antipsychotic medications, including paliperidone. Clinical manifestations include muscle rigidity, fever, altered mental status, and evidence of autonomic instability (see full Prescribing Information). Management should include immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, intensive symptomatic treatment and close medical monitoring, and treatment of any concomitant serious medical problems.

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

Tardive Dyskinesia (TD): TD is a syndrome of potentially irreversible, involuntary, dyskinetic movements that may develop in patients treated with antipsychotic medications. The risk of developing TD and the likelihood that dyskinetic movements will become irreversible are believed to increase with duration of treatment and total cumulative dose, but can develop after relatively brief treatment at low doses. Elderly female patients appeared to be at increased risk for TD, although it is impossible to predict which patients will develop the syndrome. Prescribing should be consistent with the need to minimize the risk of TD (see full Prescribing Information). Discontinue drug if clinically appropriate. The syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn.

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 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 may 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 antipsychotics. 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, fractures or other fall-related injuries. For patients, particularly the elderly, with diseases, conditions, or medications that could exacerbate these effects, assess the risk of falls when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

Leukopenia, Neutropenia and Agranulocytosis have been reported with antipsychotics, including INVEGA SUSTENNA®. In patients with a history of clinically significant low white blood cell count (WBC)/absolute neutrophil count (ANC) or drug-induced leukopenia/neutropenia, perform a complete blood count frequently during the first few months of therapy. Consider discontinuing INVEGA SUSTENNA® at the first sign of a clinically significant decline in WBC in the absence of other causative factors. Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treat promptly if such symptoms or signs occur. Discontinue INVEGA SUSTENNA® in patients with severe neutropenia (absolute neutrophil count <1000/mm³) and follow their WBC until recovery.

Hyperprolactinemia: As with other drugs that antagonize dopamine D₂ receptors, INVEGA SUSTENNA® elevates prolactin 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/P-glycoprotein (P-gp) inducers: Avoid using a strong inducer of CYP3A4 and/or P-gp (e.g. carbamazepine, rifampin, St. John’s Wort) during a 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 extrapyramidal 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% and twice placebo) were injection site reactions, somnolence/sedation, dizziness, akathisia and extrapyramidal disorder.

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

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

Brief Summary
BEFORE PRESCRIBING INVEGA SUSTENNA®, PLEASE SEE FULL PRESCRIBING INFORMATION, INCLUDING BOXED WARNING.

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. INVEGA SUSTENNA® is not approved for use in patients with dementia-related psychosis. [see Warnings and Precautions].

INDICATIONS AND USAGE
INVEGA SUSTENNA® (paliperidone palmitate) is indicated for the treatment of:
• Schizophrenia in adults [see Clinical Studies (14.1) in Full Prescribing Information].
• Schizoaffective disorder in adults as monotherapy and as an adjunct to mood stabilizers or antidepressants [see Clinical Studies (14.2) in Full Prescribing Information].

CONTRAINDICATIONS
INVEGA SUSTENNA® is contraindicated in patients with a known hyper-sensitivity to either paliperidone or risperidone, or to any of the excipients in the INVEGA SUSTENNA® formulation. Hypersensitivity reactions, including anaphylactic reactions and angioedema, have been reported in patients treated with risperidone and in patients treated with paliperidone. Paliperidone palmitate is converted to paliperidone, which is a metabolite of risperidone.

WARNINGS AND PRECAUTIONS
Increased Mortality in Elderly Patients with Dementia-Related Psychosis
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. INVEGA SUSTENNA® is not approved for the treatment of patients with dementia-related psychosis [see Boxed Warning and Warnings and Precautions].

Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis
In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly subjects with dementia, there was a higher incidence of cerebrovascular adverse reactions (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated subjects. 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 [see Boxed Warning and Warnings and Precautions].

Neuroleptic Malignant Syndrome
A potentially fatal syndrome sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs, including paliperidone. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases in which the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology. The management of NMS should include:
   (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy;
   (2) intensive symptomatic treatment and medical monitoring; and
   (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.
If a patient appears to require antipsychotic drug treatment after recovery from NMS, reinstitution of drug therapy should be closely monitored, since recurrences of NMS have been reported.

QT Prolongation
Paliperidone causes a modest increase in the corrected QT (QTc) interval. The use of paliperidone should be avoided in combination with other drugs that are known to prolong QTc including Class 1A (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic medications, antipsychotic medications (e.g., chlorpromazine, clozapine, and haloperidol), antibiotics (e.g., clindamycin, moxifloxacin), or any other class of medications known to prolong the QTc interval. Paliperidone should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias. Certain circumstances may increase the risk of the occurrence of Torsades de Pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QTc interval; and (4) presence of congenital prolongation of the QT interval.

The effects of oral paliperidone on the QT interval were evaluated in a double-blind, active-controlled (moxifloxacin 400 mg single dose), multicenter QT study in adults with schizophrenia and schizoaffective disorder, and in three placebo- and active-controlled 6-week, fixed-dose efficacy trials in adults with schizophrenia.

In the QT study (n=141), the 8 mg dose of immediate-release oral paliperidone (n=50) showed a mean placebo-subtracted increase from baseline in QTcLD of 12.3 msec (90% CI: 8.9; 15.6) on day 8 at 1.5 hours post-dose. The mean steady-state plasma concentration for this 8 mg dose of paliperidone immediate release Cmax = 113 ng/mL was more than 2-fold the exposure observed with the maximum recommended 234 mg dose of INVEGA SUSTENNA® administered in adults on the deltoid muscle (predicted median Cmax ss = 50 ng/mL). In this same study, a 4 mg dose of the immediate-release oral formulation of paliperidone, for which Cmax = 35 ng/mL, showed an increased placebo-subtracted QTcLD of 6.8 msec (90% CI: 3.6; 10.1) on day 2 at 1.5 hours post-dose.

In the three fixed-dose efficacy studies of oral paliperidone extended release in subjects with schizophrenia, electrocardiogram (ECG) measurements taken at various time points showed only one subject in the oral paliperidone 12 mg group had a change exceeding 80 msec at one time-point on Day 6 (increase of 62 msec).

In the four fixed-dose efficacy studies of INVEGA SUSTENNA® in subjects with schizophrenia and in the long-term study in subjects with schizoaffective disorder, no subject experienced a change in QTc exceeding 60 msec and no subject had a QTcLD value of > 500 msec at any time point. In the maintenance study in subjects with schizophrenia, no subject had a QTcLD change > 60 msec, and one subject had a QTcLD value of 507 msec (Bazett's QT corrected interval [QTcB] value of 480 msec); this latter subject also had a heart rate of 45 beats per minute.

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

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

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

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

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

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 ketoadidasis or hyperosmolar coma or death, have been reported in patients...
INVEGA SUSTENNA® (paliperidone palmitate) extended-release injectable suspension, for intramuscular use

treated with all atypical antipsychotics. These cases were, for the most part, seen in post-marketing clinical use and epidemiologic studies, not in clinical 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 understood. However, epidemiologic studies suggest an increased risk of hyperglycemia-related adverse reactions in patients treated with the atypical antipsychotics. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

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

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

<table>
<thead>
<tr>
<th>INVEGA SUSTENNA®</th>
<th>Placebo 39 mg</th>
<th>78 mg</th>
<th>156 mg</th>
<th>234/39 mg</th>
<th>a</th>
<th>234/156 mg</th>
<th>a</th>
<th>234/234 mg</th>
<th>a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Glucose</td>
<td>n=367</td>
<td>n=86</td>
<td>n=244</td>
<td>n=228</td>
<td>n=110</td>
<td>n=126</td>
<td>n=115</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-1.3</td>
<td>1.3</td>
<td>3.5</td>
<td>0.1</td>
<td>3.4</td>
<td>1.8</td>
<td>-0.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Proportion of Patients with Shifts | 4.6%  
(11/241) | 6.3%  
(4/64) | 6.4%  
(11/173) | 3.9%  
(6/154) | 2.5%  
(279/666) | 7.0%  
(576/866) |

* Initial deltoid injection of 234 mg followed by either 39 mg, 156 mg, or 234 mg every 4 weeks by deltoid or gluteal injection. Other dose groups (39 mg, 78 mg, and 156 mg) are from studies involving only gluteal injection. [See Clinical Studies (14.1) in Full Prescribing Information].

In a long-term open-label pharmacokinetic 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 -0.4 mg/dL at Week 29 (n=109) and +6.8 mg/dL at Week 53 (n=100). 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 +4.0 mg/dL in the placebo group (n=120).

**Dyslipidemia**

Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics. Pooled data from the four placebo-controlled (one 9-week and three 13-week), fixed-dose studies in subjects with schizophrenia are presented in Table 2.

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

<table>
<thead>
<tr>
<th>INVEGA SUSTENNA®</th>
<th>Placebo 39 mg</th>
<th>78 mg</th>
<th>156 mg</th>
<th>234/39 mg</th>
<th>a</th>
<th>234/156 mg</th>
<th>a</th>
<th>234/234 mg</th>
<th>a</th>
</tr>
</thead>
</table>
| HDL mean change from baseline (mg/dL) | n=366  
(48/581) | n=89  
(5/114) | n=244  
(5/593) | n=228     | n=110 | n=126     | n=115 |
| Cholesterol | n=366  
(48/581) | n=89  
(5/114) | n=244  
(5/593) | n=228     | n=110 | n=126     | n=115 |
| LDL mean change from baseline (mg/dL) | n=275  
(448/513) | n=80  
(6/96) | n=104  
(11/115) | n=141     | n=84 | n=108     | n=110 |
| Triglycerides | n=268  
(463/550) | n=89  
(5/114) | n=244  
(5/593) | n=228     | n=110 | n=126     | n=115 |

* Initial deltoid injection of 234 mg followed by either 39 mg, 156 mg, or 234 mg every 4 weeks by deltoid or gluteal injection. Other dose groups (39 mg, 78 mg, and 156 mg) are from studies involving only gluteal injection. [See Clinical Studies (14.1) in Full Prescribing Information].

The mean changes from baseline in lipid 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 subjects with schizoaffective disorder are presented in Table 4.

Table 3: Change in Fasting Lipids from Long-Term Open-Label Pharmacokinetic and Safety Study in Subjects with Schizophrenia

<table>
<thead>
<tr>
<th>INVEGA SUSTENNA®</th>
<th>Week 29</th>
<th>Week 53</th>
</tr>
</thead>
</table>
| Cholesterol | n=112  
(6/51) | n=100  
(3/49) |
| Change from baseline | -2.7   
(7/84) | -2.3   
(4/69) |
| HDL | n=112  
(6/51) | n=98  
(3/49) |
| Change from baseline | -0.8   
(7/84) | -2.6   
(4/69) |
| Triglycerides | n=112  
(6/51) | n=100  
(3/49) |
| Change from baseline | 16.2   
(7/84) | 37.4   
(4/69) |

The mean changes from baseline in lipid 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 subjects with schizoaffective disorder are presented in Table 4.

Table 4: Change in Fasting Lipids from an Open-Label and Double-Blind Periods of a Long-Term Study in Subjects with Schizoaffective Disorder

<table>
<thead>
<tr>
<th>INVEGA SUSTENNA®</th>
<th>Placebo</th>
<th>INVEGA SUSTENNA®</th>
</tr>
</thead>
</table>
| Cholesterol | n=198  
(6/31) | n=119  
(3/29) |
| Change from baseline | -3.9  
(5/58) | -4.2  
(2/26) |
| HDL | n=198  
(6/31) | n=119  
(3/29) |
| Change from baseline | -2.7  
(5/58) | -2.8  
(2/26) |
In a long-term open-label pharmacokinetic and safety study in which the highest dose groups (78 mg, 156 mg, and 234 mg) were treated weekly for 9 to 13-week, Fixed-Dose Studies in Subjects with Schizophrenia

Table 5: Mean Change in Body Weight (kg) and the Proportion of Subjects with a >2% Gain in Body Weight

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Mean Change from Baseline</th>
<th>Proportion of Subjects with a &gt;2% Gain in Body Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-0.2 kg</td>
<td>0%</td>
</tr>
<tr>
<td>39 mg</td>
<td>0.4 kg</td>
<td>4%</td>
</tr>
<tr>
<td>78 mg</td>
<td>0.8 kg</td>
<td>9%</td>
</tr>
<tr>
<td>156 mg</td>
<td>1.4 kg</td>
<td>11%</td>
</tr>
<tr>
<td>234 mg</td>
<td>1.4 kg</td>
<td>12%</td>
</tr>
</tbody>
</table>

INVEGA SUSTENNA®

INVEGA SUSTENNA® is available in a single-patient, fixed-dose, extended-release injectable suspension, for intramuscular use.

Tissue culture experiments indicate that approximately one-third of human breast cancer, lymphoma, and melanoma cells have prolactin receptors. Chronic administration of prolactin to animals has been associated with mammary gland, breast gland, and skin hyperplasia. In vitro studies have shown an association between chronic administration of prolactin and breast cancer in mice and rats [see Nonclinical Toxicology (13.1) in Full Prescribing Information].

In the absence of other causative factors, the diagnosis of prolactinomas should be considered.

INVEGA SUSTENNA® is contraindicated in patients with a prolactinoma.

INVEGA SUSTENNA® is associated with a mean change in weight of +2.2 kg at Week 29 (n=134) and +4.3 kg at Week 53 (n=113).

During the initial 25-week open-label period of a long-term study in subjects with schizophrenia disorder, INVEGA SUSTENNA® was associated with a mean change in weight of +2.2 kg and 18.4% of subjects had an increase in body weight of ≥ 7% (n=835). At the endpoint of the subsequent 15-month double-blind period, INVEGA SUSTENNA® was associated with a mean change in weight of -0.2 kg and 13.0% of subjects had an increase in body weight of ≥ 7% (n=161); the placebo group had a mean change in weight of -0.8 kg and 6.0% of subjects had an increase in body weight of ≥ 7% (n=168).

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% (4/1293) 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% (0/510) of subjects treated with placebo. In the four fixed-dose efficacy studies in subjects with schizophrenia, orthostatic hypotension and syncope was reported as an adverse event by < 1% (2/1293) of INVEGA SUSTENNA®-treated subjects compared to 0% (0/510) with placebo. Incidences of orthostatic hypotension and syncope in the long-term studies in subjects with schizophrenia and schizoaffective disorder were similar to those observed in the short-term studies.

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., dehydration, hypovolemia, 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 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 predispose them to falls, INVEGA SUSTENNA® should be used with caution. Falls and resulting fractures are common occurrences in the general population and patients may have underlying risk factors.

Leukopenia, Neutropenia, and Agranulocytosis

In clinical trial and/or postmarketing experience, events of leukopenia and neutropenia have been reported temporarily related to antipsychotic agents, including INVEGA SUSTENNA®. Agranulocytosis has also been reported. Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC)/absolute neutrophil count (ANC) and history of drug-induced leukopenia/neutropenia. In patients with a history of a clinically significant low WBC/ANC or a drug-induced leukopenia/neutropenia, perform a complete blood count (CBC) frequently during the first few months of therapy. In such patients, consider discontinuation of 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. INVEGA SUSTENNA® was associated with an increase in neutrophils in patients with severe neutropenia (absolute neutrophil count < 1000/mm3) and follow their WBC until recovery.

Hyperprolactinemia

In clinical trial and/or postmarketing experience, elevations of prolactin to above the reference range (N=275) in males and N=239) in females have been reported associated with a mean change in prolactin of 72.4 (46.5) ng/mL in females (N=358). At the end of the open-label phase, mean (SD) prolactin values were 24.7 (22.5) ng/mL in males (N=480) and 59.5 (38.1) ng/mL in females (N=333). During the open-label phases 49.2% of males and 47.1% of males experienced elevations of prolactin above the reference range relative to baseline, and a higher proportion of female patients experienced potentially prolactin-related adverse reactions compared to males (5.3% vs. 1.8%). Amenorrhea (2.5%) in females and no single potentially prolactin-related adverse reaction in males were observed with a rate greater than 2%.

Schizoaffective Disorder

In a long-term maintenance trial of INVEGA SUSTENNA® in patients with schizoaffective disorder (Study SCA-3004) see Clinical Studies (14.2), elevations of prolactin to above the 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 a higher percentage of the patients in the INVEGA SUSTENNA® group than those in the placebo group in males (51.9% vs. 29.0%) and in females (50.5% vs. 42.9%). During the double-blind phase, 4 females (4.2%) in the INVEGA SUSTENNA® group experienced potentially prolactin-related adverse reactions (amenorrhea N=2; galactorrhea N=1; menstruation irregular N=1), while 2 females (2.2%) in the placebo group experienced potentially prolactin-related adverse reactions (amenorrhea N=1; galactorrhea N=1). One male (0.9%) in the INVEGA SUSTENNA® group experienced erectile dysfunction and 1 male (0.9%) in placebo group experienced gynecomastia.

Prior to the double-blind phase (during the 33-week open-label phase of the long-term maintenance trial), the mean (SD) prolactin values were 14.9 (22.3) ng/mL in males (N=480) and 35.2 (38.8) ng/mL in females (N=358). At the end of the open-label phase, mean (SD) prolactin values were 24.7 (22.5) ng/mL in males (N=480) and 59.5 (38.1) ng/mL in females (N=333). At the end of the open-label phases 49.2% of males and 47.1% of patients experienced elevations of prolactin above the reference range relative to baseline, and a higher proportion of female patients experienced potentially prolactin-related adverse reactions compared to males (5.3% vs. 1.8%). Amenorrhea (2.5%) in females and no single potentially prolactin-related adverse reaction in males were observed with a rate greater than 2%.

Hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects.

Potential for Cognitive and Motor Impairment

Somnolence, sedation, and dizziness were reported as adverse reactions in patients treated with INVEGA SUSTENNA® (see Adverse Reactions). Antipsychotics, including INVEGA SUSTENNA®, have the potential to impair cognitive and motor performance. Patients should be cautioned about the risk of accidents while driving or operating machinery or operating a motor vehicle, until they are reasonably certain that paliperidone therapy does not adversely affect them.

Seizures

Activity in four fixed-dose double-blind placebo-controlled studies in subjects with schizophrenia, <1% (1/1293) of subjects treated with INVEGA SUSTENNA® in the recommended dose range of 39 mg to 234 mg experienced an adverse event of convulsion compared with <1% (1/510) 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.

Disphagia
Esophageal motility and aspiration have been associated with antipsychotic drug use. INVEGA SUSTENNA® and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Priapism
Drugs with alpha-adrenergic blocking effects have been reported to induce priapism. Although no cases of priapism have been reported in clinical trials with INVEGA SUSTENNA®, priapism has been reported with oral paliperidone during postmarketing surveillance. Severe priapism may require surgical intervention.

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

ADVERSE REACTIONS

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

- Increased mortality in elderly patients with dementia-related psychosis [see Boxed Warning and Warnings and Precautions]
- Cerebrovascular adverse reactions, including stroke, in elderly patients with dementia-related psychosis [see Warnings and Precautions]
- Neuroleptic malignant syndrome [see Warnings and Precautions]
- QT prolongation [see Warnings and Precautions]
- Tardive dyskinesia [see Warnings and Precautions]
- Metabolic changes [see Warnings and Precautions]
- Orthostatic hypotension and syncope [see Warnings and Precautions]
- Falls [see Warnings and Precautions]
- Leukopenia, neutropenia, and agranulocytosis [see Warnings and Precautions]

Clinical Trials Experience

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

Patient Exposure

The data described in this section are derived from a clinical trial database consisting of a total of 3817 subjects (approximately 1705 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, 1283 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 trial (median exposure 229 days during the initial 32-week open-label phase of this study, of whom 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 [deltoid-gluteal] cross-over trial). One of the 13-week studies included a 234 mg INVEGA SUSTENNA® initiation dose followed by treatment with either 39 mg, 156 mg, or 234 mg every 4 weeks.

The safety of INVEGA SUSTENNA® was also evaluated in a 15-month, long-term study comparing INVEGA SUSTENNA® to selected oral antipsychotic therapies in adult subjects with schizophrenia. A total of 226 subjects received INVEGA SUSTENNA® during the 15-month, open-label period of this study; 218 subjects received selected oral antipsychotic therapies. The safety of INVEGA SUSTENNA® was similar to that seen in previous double-blind, placebo-controlled trials and similar 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 687 subjects received INVEGA SUSTENNA® during the initial 25-week open-label period of this study (median exposure 143 days). Of these subjects, 214 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 in the INVEGA SUSTENNA® than the placebo group (a 2% difference or more between groups) were weight increased, nasopharyngitis, headache, hyperprolactinemia, and pyrexia.

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

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

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

Discontinuation of Treatment Due to Adverse Events: The percentage of subjects who discontinued due to adverse events in the four fixed-dose, double-blind, placebo-controlled schizophrenia trials were similar for INVEGA SUSTENNA®- and placebo-treated subjects. The percentage of subjects who discontinued due to adverse events in the open-label period of the long-term study in subjects with schizoaffective disorder was 7.5%. During the double-blind, placebo-controlled period of that study, the percentages of subjects who discontinued due to adverse events were 5.5% and 1.8% in INVEGA SUSTENNA®- and placebo-treated subjects, respectively.

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

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

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placeboa (N=510)</th>
<th>39 mg (N=130)</th>
<th>78 mg (N=202)</th>
<th>156 mg (N=163)</th>
<th>234 mg (N=165)</th>
<th>234 mg/39 mgb (N=163)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total percentage of subjects with adverse reactions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal involuntary movements/adverse reactions</td>
<td>70</td>
<td>75</td>
<td>68</td>
<td>69</td>
<td>63</td>
<td>60</td>
</tr>
<tr>
<td>Abdominal discomfort/abdominal pain upper</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Toothache</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4</td>
<td>5</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrialia</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Injection site reactions</td>
<td>2</td>
<td>6</td>
<td>9</td>
<td>7</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>&lt;1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>&lt;1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight increased</td>
<td>1</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Increased</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Musculoskeletal stiffness</td>
<td>1</td>
<td>1</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Myalgia</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>&lt;1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Akathisia</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1</td>
<td>6</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Extrapyramidal disorder</td>
<td>1</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>12</td>
<td>11</td>
<td>15</td>
<td>11</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Somnolence/sedation</td>
<td>3</td>
<td>5</td>
<td>7</td>
<td>4</td>
<td>1</td>
<td>5</td>
</tr>
</tbody>
</table>

Extended-release injectable suspension, for intramuscular use

INVEGA SUSTENNA® (paliperidone palmitate)
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 (continued)

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Placebo (N=150)</th>
<th>39 mg (N=161)</th>
<th>78 mg (N=160)</th>
<th>156 mg (N=163)</th>
<th>234 mg (N=164)</th>
<th>Overall Percentage of Placebo-Treated Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic reactions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cutaneous reactions</td>
<td>1 (1.0%)</td>
<td>1 (0.6%)</td>
<td>1 (0.6%)</td>
<td>1 (0.6%)</td>
<td>1 (0.6%)</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>2 (1.4%)</td>
<td>2 (1.2%)</td>
<td>2 (1.2%)</td>
<td>2 (1.2%)</td>
<td>2 (1.2%)</td>
<td>2 (1.4%)</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>1 (0.7%)</td>
<td>1 (0.6%)</td>
<td>1 (0.6%)</td>
<td>1 (0.6%)</td>
<td>1 (0.6%)</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>1 (1.0%)</td>
<td>1 (0.6%)</td>
<td>1 (0.6%)</td>
<td>1 (0.6%)</td>
<td>1 (0.6%)</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>1 (0.7%)</td>
<td>1 (0.6%)</td>
<td>1 (0.6%)</td>
<td>1 (0.6%)</td>
<td>1 (0.6%)</td>
<td>1 (0.7%)</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Scale</th>
<th>Placebo (N=262)</th>
<th>39 mg (N=130)</th>
<th>78 mg (N=130)</th>
<th>156 mg (N=130)</th>
<th>234 mg (N=130)</th>
<th>Overall Percentage of Placebo-Treated Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinsonism</td>
<td>10 (3.8%)</td>
<td>12 (9.2%)</td>
<td>10 (7.7%)</td>
<td>6 (4.6%)</td>
<td>11 (8.5%)</td>
<td>11 (4.2%)</td>
</tr>
<tr>
<td>Akathisia</td>
<td>5 (1.9%)</td>
<td>5 (3.8%)</td>
<td>6 (4.6%)</td>
<td>5 (3.8%)</td>
<td>6 (4.6%)</td>
<td>6 (2.3%)</td>
</tr>
<tr>
<td>Dyskinesia</td>
<td>3 (1.2%)</td>
<td>4 (3.1%)</td>
<td>4 (3.1%)</td>
<td>3 (2.3%)</td>
<td>4 (3.1%)</td>
<td>4 (1.5%)</td>
</tr>
<tr>
<td>Use of Anticholinergic Medications</td>
<td>12 (4.6%)</td>
<td>10 (7.7%)</td>
<td>12 (9.2%)</td>
<td>11 (8.5%)</td>
<td>12 (9.2%)</td>
<td>12 (4.6%)</td>
</tr>
</tbody>
</table>

For Parkinsonism, percent of subjects with Simpson-Angus 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 score > 2 at endpoint

For Dyskinesia, 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 Involuntary Movement Scale at endpoint

For percent of subjects who received anticholinergic medications to treat EPS

The results from all 4 fixed-dose, double-blind, placebo-controlled trials in schizophrenia were higher in the INVEGA SUSTENNA® 156 mg group (18% and 11%, respectively) than in the INVEGA SUSTENNA® 78 mg group (9% and 5%, respectively) and placebo group (7% and 4%, respectively).
INVEGA SUSTENNA® (paliperidone palmitate) extended-release injectable suspension, for intramuscular use

In the 13-week study involving 234 mg initiation dosing in subjects with schizophrenia, exacerbations of redness, swelling, induration, and pain were reported in 15% of subjects treated with INVEGA SUSTENNA® due to local irritation at the injection site. In studies with orally administered paliperidone, approximately 95-100% of subjects in both the INVEGA SUSTENNA® and placebo groups. At Day 92, investigators rated absence of redness, swelling, induration, and pain at between 95-100% of subjects in both the INVEGA SUSTENNA® and placebo groups. 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:

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: pharyngodyngarygeal pain, pneumonia aspiration
Skin and subcutaneous tissue disorders: rash papular
Vascular disorders: hypotension, 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 uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: angioedema, ileus, somnambulism, swollen tongue, thrombotic thrombocytopenic purpura, urinary incontinence, and urinary retention.

Cases of anaphylactic reaction after injection with INVEGA SUSTENNA® have been reported during postmarketing experience in patients who have previously tolerated oral risperidone or oral paliperidone. Paliperidone is the major active metabolite of risperidone. Adverse reactions reported with oral risperidone and risperidone long-acting injection can be found in the Adverse Reactions sections of the package inserts for those products.

DRUG INTERACTIONS

Drugs Having Clinically Important Interactions with INVEGA SUSTENNA®

Because paliperidone palmitate is hydrolyzed to paliperidone [see Clinical Pharmacology (12.3) in Full Prescribing Information], results from studies with oral paliperidone should be taken into consideration when assessing drug-drug interaction potential.

Table 9: Clinically Important Drug Interactions with INVEGA SUSTENNA®

<table>
<thead>
<tr>
<th>Dopamine Agonist</th>
<th>Clinical Impact</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paliperidone may antagonize the effect of levodopa and other dopamine agonist</td>
<td>Monitor and manage patient as clinically appropriate</td>
<td>Levodopa, bromocriptine, ropinirole and pramipexole</td>
</tr>
</tbody>
</table>

Drugs Having No Clinically Important Interactions with INVEGA SUSTENNA®

Clinically meaningful pharmacokinetic interaction between INVEGA SUSTENNA® and valproate (including valproic acid and divalproex sodium) is not expected. Based on pharmacokinetic studies with oral paliperidone, no dosage adjustment of INVEGA SUSTENNA® is required when administered with valproate [see Clinical Pharmacology (12.3) in Full Prescribing Information]. Additionally, no dosage adjustment is necessary for valproate when co-administered with INVEGA SUSTENNA® [see Clinical Pharmacology (12.3) in Full Prescribing Information].

Pharmacokinetic interaction between lithium and INVEGA SUSTENNA® is also unlikely. Paliperidone is not expected to cause clinically important pharmacokinetic interactions with drugs that are metabolized by cytochrome P450 isozymes. In vitro studies indicate that CYP2D6 and CYP3A4 may be involved in paliperidone metabolism; however, there is no evidence in vivo that inhibitors of these enzymes significantly affect the metabolism of paliperidone. Paliperidone is not a substrate of CYP1A2, CYP2A6, CYP2C9, and CYP2C19; an interaction with inhibitors or inducers of these isozymes is unlikely. [see Clinical Pharmacology (12.3) in Full Prescribing Information].

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to paliperidone during pregnancy. Healthcare providers are encouraged to register patients by contacting the National Pregnancy Registry for Atypical Antipsychotics at 1-888-961-2988 or online at womensmentalhealth.org/cclinical-and-research-programs/pregnancyregistry/.

Risk Summary

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery [see Clinical Considerations]. Overall, available data from published epidemiologic studies of pregnant women exposed to paliperidone have not established a drug-associated risk for major birth defects, miscarriage, or adverse maternal or fetal outcomes [see Data]. There are risks to the mother associated with untreated schizophrenia and with exposure to antipsychotics, including INVEGA SUSTENNA® administered before pregnancy or anytime during pregnancy is not known.

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

In animal reproduction studies, there were no treatment-related effects on the offspring when pregnant rats were injected intramuscularly with paliperidone palmitate during the period of organogenesis at doses up to 10 times the maximum recommended human dose (MRHD) of 234 mg paliperidone based on mg/m² body surface area. There were no increases in fetal abnormalities 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 paliperidone based on mg/m² body surface area. Additional reproduction toxicity studies were conducted with orally administered risperidone, which is extensively converted to paliperidone (see Animal data).

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

There is a risk to the mother from untreated schizophrenia, including increased risk of relapse, hospitalization, and suicide. Schizophrenia and bipolar I disorder are associated with increased adverse perinatal outcomes, including preterm birth. It is not known if this is a direct result of the illness or other comorbid factors.

Fetal/Neonatal Adverse Reactions

Examples Levodopa, bromocriptine, ropinirole and pramipexole

Intervention Monitor orthostatic vital signs in patients who are at risk for orthostatic hypotension [see Warnings and Precautions]

Examples Nitrates

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<tr>
<th>Clinical Impact</th>
<th>Intervention</th>
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<tr>
<td>The concomitant use of paliperidone and strong inducers of CYP3A4 and P-gp may decrease the exposure of paliperidone [see Clinical Pharmacology (12.3) in Full Prescribing Information]</td>
<td>Avoid using CYP3A4 and/or P-gp inducers with INVEGA SUSTENNA® during the 1-month dosing interval, if possible. If administering a strong inducer is necessary, consider managing the patient using paliperidone extended release tablets [see Dosage and Administration (2.5) in Full Prescribing Information]</td>
<td>Carbamazepine, rifampin, St John's Wort</td>
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INVEGA SUSTENNA® (paliperidone palmitate) extended-release injectable suspension, for intramuscular use

Data

Human Data

Published data from observational studies, birth registries, and case reports on the use of atypical antipsychotics during pregnancy do not report a clear association with antipsychotics and major birth defects. A prospective observational study including 8 women treated with risperidone, the parent compound of paliperidone, demonstrated placental passage of risperidone and paliperidone. A retrospective cohort study from a Medicaid database of 92,634 women exposed to antipsychotics during pregnancy did not indicate an overall increased risk for major birth defects. There was a small increase in the risk of major birth defects (RR = 1.26, 95% CI 1.02-1.58) and of cardiac malformations (RRs = 1.12, 95% CI 0.89-1.41) in a subgroup of 1968 women exposed to the parent compound of paliperidone, risperidone, during the first trimester of pregnancy; however, there is no mechanism of action to explain the difference in malformation rates.

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 234 mg paliperidone based on mg/m² body surface area.

In animal reproduction studies, there were no increases in fetal abnormalities when pregnant rats and rabbits were treated orally with paliperidone during the period of organogenesis with up to 8 times the MRHD of 12 mg based on mg/m² body surface area.

Additional reproductive 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 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 6 times the MRHD based on mg/m² body surface area, reached adulthood, learning was impaired. Increased neuronal cell death occurred in the fetal brains of the offspring of pregnant rats treated at 95 to 1.7 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 of 0.5 to 1.2 times the MRHD; the postnatal development and growth of the offspring was impaired. Increased neuronal cell death occurred in the fetal brains of 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 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 6 times the MRHD based on mg/m² body surface area, reached adulthood, learning was impaired. Increased neuronal cell death occurred in the fetal brains of the offspring of pregnant rats treated at 95 to 1.7 times the MRHD; the postnatal development and growth of the offspring was delayed.

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

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 Lewy Body Dementia 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.

OVERDOSAGE

Human Experience

No cases of overdose were reported in premarketing studies with INVEGA SUSTENNA®. Paliperidone overdose should be considered a medical emergency requiring immediate life support measures. There is no specific antidote to paliperidone. Induced emesis or gastric lavage is probably not useful since paliperidone is extensively metabolized and little unmetabolized drug is likely to remain unabsorbed. Gastric lavage may be useful to remove unabsorbed drug if it is to be administered within 1 hour of ingestion.

No deaths have been reported with paliperidone overdose, and signs and symptoms included extrapyramidal symptoms and gait unsteadiness. Other potential signs and symptoms include those resulting from an exaggeration of paliperidone’s known pharmacologic effects, i.e., drowsiness and sedation, tachycardia and hypotension, and QT prolongation. Torsades de pointes and ventricular fibrillation have been reported in a patient in the setting of overdose with oral paliperidone.

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

Management of Overdose

Contact a Certified Poison Control Center for the most up to date information on the management of INVEGA SUSTENNA® overdose (1-800-222-1222 or www.poison.org). Provide supportive care, including close medical supervision and monitoring. Treatment should consist of general measures employed in the management of overdose with any drug. Consider the possibility of multiple drug overdosage. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. Use supportive and symptomatic measures. There is no specific antidote to paliperidone.

Consider the prolonged-release characteristics of INVEGA SUSTENNA® and the long apparent half-life of paliperidone when assessing treatment needs and recovery.

INVEGA SUSTENNA® (paliperidone palmitate) Extended-Release Injectable Suspension

Product of Ireland

Manufactured by: Janssen Pharmaceutical NV

Beershe, Belgium

Manufactured for: Janssen Pharmaceuticals, Inc.

Thruelle, NJ 08560

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

Psychiatry 2021: Team Psychiatry

John J. Miller, MD | Editor in Chief

Individuals with mental illness continue to struggle with access to treatment in the United States, including in metropolitan hubs. Despite the huge unmet need for additional psychiatrists in the United States, the number of graduating medical students choosing psychiatry as their specialty training sadly remains quite low. Thomas et al estimated that approximately 96% of the 3140 US counties had an unmet need for practicing psychiatrists, and this need was higher in rural areas and areas with low per capita income. In 2013, 70% of US psychiatrists were over the age of 50, suggesting this shortage will only increase as current practitioners retire in the years ahead. I live in Exeter, New Hampshire, a mere hour north of Boston, Massachusetts, where the waiting time for an initial outpatient psychiatric evaluation is anywhere from 2 to 6 months.

I was introduced to my first psychiatric mental health advanced practice registered nurse (PMH-APRN) when I joined a private psychiatric group practice in 1995 in Newburyport, Massachusetts. This was a multispecialty outpatient practice with a wide range of clinical specialties: therapists of various degrees, a neuropsychologist, 6 psychiatrists, and a psychiatric nurse practitioner (psych NP)—the title used at that time). To be honest, I was clueless that this advanced nursing practice clinical psychiatry—and to prescribe medications no less! The 6 psychiatrists who had worked with this psych NP for years continually reassured me that the nurse was clinically solid and competent. Over time I came to the same conclusion. We became, and remain, colleagues. I now refer patients to her without any reservation.

Over the next 10 years I served as the supervising psychologist to 5 PMH-APRNs in various clinical settings in Newburyport, as a legal supervision contract was required by the Massachusetts Board of Registration in Nursing. For the first 5 years, I met with these PMH-APRNs weekly. After relocating to New Hampshire and shifting my practice to a community mental health center (CMHC) in 2007, my supervision transformed to a consultation role per the New Hampshire Board of Nursing requirements. I continue to thoroughly enjoy these consultation meetings, and I remain impressed with these individuals’ clinical skills, eagerness to learn, and commitment to improve their patients’ functioning.

In New Hampshire, PMH-APRNs fill a huge void by providing psychiatric treatment that otherwise would not exist. I know this from direct personal experience. There are 10 CMHCs in New Hampshire, and collectively they employ roughly equal numbers of PMH-APRNs and psychiatrists. At our CMHC, we have 9 psychiatrists and 4 PMH-APRNs. We have

Approximately 96% of the 3140 US counties had an unmet need for practicing psychiatrists.

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<td>25 Early Warnings: Neuropsychiatric Manifestations of Huntington Disease Rajesh R. Tampi, MD, MS, DFAPA, DFAAGP, Monica Weber, MBA, MSAA, CCTP, LISW-S, and Gilbert A. Masterson, MD</td>
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increased our access in the community by having these PMH-APRNs work in our community hospital’s emergency department, spend time at the local homeless shelter, and schedule onsite hours at nearby community health centers (CHCs). Additionally, the waiting time for an initial evaluation has decreased.

Similarly, throughout the United States, CHCs and CMHCs experience a disproportional shortage of psychiatric prescribers. Over the past 20 years, one growing resource has been the utilization of PMH-APRNs. In 2010, the American Psychiatric Nurses Association chose this new title and acronym to replace 2 older titles: psychiatric nurse practitioner and psychiatric clinical nurse specialist. For the interested reader, Mary D. Moller, DNP, ARNP, PMHCNS-BC, CPRP, FAAN, provides a historical review of the specialty of PMH-APRN from its beginnings at Rutgers University in 1954 to its current status.3

Currently, each state maintains its own licensing requirements and range of prescription privileges for PMH-APRNs. Yang et al reviewed the number of mental health-related visits at CHCs during the years 2006 through 2011 in states where nurse practitioners had “independent practice authority” (NP-IPA), as compared with states where they did not.4 Not surprisingly, in states with NP-IPA, there was a significant increase in mental health-related treatment/prescriptions by the NPs, which demonstrates increased utilization of NPs for mental health visits in CHCs. Most recently, in the January 2021 issue of Psychiatric Services, Frissora and Ranz from the Department of Psychiatry at Columbia University Medical Center in New York discuss how PMH-APRNs serve an important role in providing access to psychiatric treatment, especially in rural areas, urban neighborhoods, CHCs, and other settings with significant unmet mental health access. The authors describe their development of a federally qualified health center’s Community Psychiatry Nurse Practitioner Fellowship, and the success of this program.5

I have lectured in 47 states, including many rural and economically deprived areas. In all clinical settings, but especially these, the majority of frontline psychiatric treatment is delivered by PMH-APRNs. The local primary care physicians, clinics, and hospitals count on them. In my view, PMH-APRNs have become well-needed colleagues that are an integral part of our national health care system and allow us to fulfill our primary oath as physicians: “Do no harm.” There simply are not enough of us psychiatrists in the United States. Pecorino expresses this succinctly: “PMH-APRNs have become an integral part of health care in the United States.”

What is important is that each professional member on Team Psychiatry knows what we each know, what we don’t know, and to seek out consultation as needed. Each of us has unique training, responsibilities, limitations, and value. Collectively we can rise to the challenge of providing quality mental health care in all treatment settings in the United States.

REFERENCES

My first appointment was with the APRN, and I left feeling good about my new health care team. PMH-APRNs have become an integral part of health care in the United States. For us in psychiatry, I consider them an integral part of our treatment teams: psychiatrists, PMH-APRNs, psychiatric nurses, psychologists, neuropsychologists, pharmacists, therapists, case managers, occupational therapists, emergency service clinicians, students in training of all types, and more. What is important is that each professional member on Team Psychiatry knows what we each know, what we don’t know, and to seek out consultation as needed.
One year with COVID-19

Continued from Cover

Approximately 83 million people have been infected by COVID-19 and 1.8 million souls worldwide were lost, according to The New York Times and several other news outlets. In 2020, the United States alone saw approximately 19 million cases of individuals infected with COVID-19 and around 350,000 deaths. The highest single-day death toll in the United States occurred on December 30, 2020, on which 3808 individuals died. The closest the country has ever come to that astonishing number was September 16, 1928, when about 3000 individuals died from the Okeechobee hurricane. Figure 1 puts the death toll in further perspective, by comparing death rates from other events.

Lessons Learned From My Recovery
1, too, became a part of these statistics—contracting COVID-19 in March 2020. After my hospitalization, I still had residual symptoms, including shortness of breath, fatigue, and decreased exercise tolerance. I was concerned that I would not be able to work and about the effect this would have on my patients. I wondered when—if—I would be able to work at the same pre–COVID-19 level of intensity. Would my symptoms be lifelong? Like so many Americans, I worried about the potential financial strain. I knew that if I was to get back to being a psychiatrist, I needed to get my shortness of breath and fatigue under better control. To help improve my lung function, strengthen my exercise tolerance, and for my own mental health, I went for progressively longer walks with my French bulldog, Principe Azul. Gradually, my shortness of breath improved, but not to the point where I felt able to work onsite at the hospital.

Fortunately, I was offered the opportunity to work remotely. Not only was this my first time working in the realm of telepsychiatry, but I was the test pilot for my department. Suffice to say there was a learning curve, but I already had an interest in this area of psychiatry. Although I was not fully recovered, I improved enough to see my patients virtually. I believe work has multiple therapeutic benefits and is part of who I am.

My journey has been filled with one small step followed by another, each heading in the right direction. To date I continue to experience shortness of breath, chest tightness, periodic fatigue, and decreased exercise tolerance. My recovery has been a process, and the same will be true about our country’s slow and hopefully steady march out of this dark chapter.

A Cautionary Yet Hopeful Tale of 2 New Years
Although many of us were surprised by the severity and devastation of COVID-19, there is evidence that our top officials knew more in the early days of the pandemic than we suspected. Several news networks have reported that former President Donald Trump received warnings about COVID-19’s lethality and its serious political and economic consequences as early as January 2020, yet the administration purposely downplayed the virus’ threat. Unfortunately, this tactic resulted in the lack of a unified and scientific approach to address the pandemic. On the other hand, 2021 kicked off with significant positive events: 2 mRNA COVID-19 vaccines (Pfizer/BioNTech and Moderna) continue to be rolled out, and 2 additional COVID-19 vaccines (Johnson & Johnson’s double-stranded DNA single shot and AstraZeneca’s chimpanzee adenovirus 2 shot COVID-19) are likely to be released as this issue goes to print. Newly installed President Joe Biden has embarked on initiatives to conquer the virus. Yet, there have been several days in 2021 for which the reported daily death toll surpassed 2020’s highest daily death toll. We still have a long way to go.

Here’s Looking at You, Kid: Health Care Workers
In March 2020, when New York City was the epicenter of the pandemic, both New York Governor Andrew Cuomo and New York City Mayor Bill de Blasio requested help from health care retirees and medical students to staff the front lines. Sure enough, one of the nurses who cared for me when I was hospitalized was a retired US Army nurse. I was relieved that a seasoned peer came out of retirement to help keep me alive.

We are a society that often dismisses and neglects its older and more experienced individuals (and yet they ran to our rescue). Perhaps that is why our most vulnerable citizens in nursing homes were first to be devastated by this virus. It is crucial that we protect the vulnerable and honor the experienced among us.

The level of professionalism and dedication among health care workers shined throughout the pandemic. With loved ones no longer allowed to visit patients, health care workers took on the role of surrogate family, comforting patients with COVID-19 and other medical issues as they confronted their own mortality. They also went the extra mile to update families and loved ones, so they did not feel so alone and helpless. This level of commitment has not come without cost. Stress, anxiety, depression, and grief are among the constellation of symptoms affecting health care workers. They have faced the constant fear of contracting the virus and bringing it home to a loved one. They witnessed the suffering of people with COVID-19, as well as prolonged separation from family and loved ones.

Although there has been some recognition of the efforts and risks, support comes in waves. Early in the pandemic we heard and saw nightly clapping for health care workers in New York City and around the country. It remains unclear what the new administration will do to meaningfully recognize this service via financial and nonfinancial compensation (ie, hazard pay, tax incentives, student loan forgiveness, a national monument to commemorate those
we lost to COVID-19 and recognize our frontline workers, etc.\textsuperscript{17}

\textbf{“COVID Karens,” Antimaskers, and Pandemic Deniers}

The pandemic also put the spotlight on those who refused to listen to science. Our country saw the proliferation of antimaskers who vocally denied the severity of the virus. They defied social distancing recommendations, gathered in large numbers, and caused superspreader events.\textsuperscript{18,19}

As psychiatrists, we have explored and discussed the multitude of reasons for the antimask campaign.\textsuperscript{20} Some of these individuals closely followed the lead of President Trump, who continued to dismiss the severity of the virus, even when he contracted it. Some have a sense of entitlement—the “COVID Karens,” who appeared regularly in videos on the news. Others suffered from pandemic fatigue or experienced significant financial or jobs loss because of the pandemic, or simply did not want to have to confront the fear and ramifications of COVID-19.\textsuperscript{21}

Unfortunately, many of these individuals took their plight to the ones fighting the virus on the front lines. There are documented incidents of COVID-19 nonbelievers blocking, harassing, and interfering with health care workers’ jobs, adding insult to injury. Health care workers have had to not only rise above this noise but also manage their own countertransference.

Figure 2


\textbf{Science and Strategies for the Long Haul}

Since the onset of the pandemic, we have learned a great deal more about this virus. We now know clinical presentations are variable in severity, ranging from asymptomatic to more severe cases.\textsuperscript{22,23}

Similarly, we recognize that the effects of COVID-19 is not limited to an acute insult; sometimes the virus haunts its host long after infection appears to be gone. Huang et al published a cohort study of patients 6 months after their acute infection.\textsuperscript{24} They found patients continued to suffer from fatigue, muscle weakness, sleep difficulties, anxiety, and depression. Further studies are needed to gain insight into understanding of the long-term effects of the virus and how to address them. Like my recovery, this will require small, continued steps.

\textbf{Unraveling Neuropsychiatric Manifestations}

Regardless of COVID-19 infection or history of mental illness, there has been a communal experience of posttraumatic stress disorder, anxiety, depression, hopelessness, and despair.\textsuperscript{25,26,27} These symptoms may not necessarily reach DSM-5 diagnostic thresholds but nonetheless have been present for many people throughout the pandemic.\textsuperscript{28}

In addition, there is growing literature that suggests some acutely ill patients may also develop neuropsychiatric symptoms.\textsuperscript{21,27,29} Multiple potential mechanisms have been proposed by which severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) induces mental status changes.\textsuperscript{30,31} Currently, there are no official guidelines on the management of these symptoms in patients with COVID-19.\textsuperscript{28}

\textbf{Mental Illness During the COVID-19 Pandemic}

Researchers have found that individuals with psychiatric disorders are more susceptible to COVID-19 and its complications. In one study, for example, investigators found that patients with a recent diagnosis of a mental disorder had a significantly increased risk of COVID-19 infection. The effect was strongest for depression and schizophrenia, with an adjusted odds ratio of 7.64 and 7.34, respectively.\textsuperscript{29} To protect our patients, we need to do more to secure their overall well-being, such as ensuring proper housing, teaching coping skills, and boosting resilience.

Fortunately, not all patients with mental illnesses have experienced a worsening of their psychiatric symptoms.\textsuperscript{30-32} In my clinical practice, for example, some patients with anxiety spectrum disorders have reported no appreciable worsening of their anxiety during the pandemic. Instead, they noted they felt like the rest of the world was catching up to their baseline daily level of anxiety. Perhaps the pandemic has taught us to better help our patients celebrate their strengths.

\textbf{The Deepening Divide of Discrimination}

Although the virus does not discriminate, it has disproportionately affected minorities.\textsuperscript{33} Black people and Latinos have died at 3.6 times and 2.5 times, respectively, the rate of White people (Figures 2, 3).\textsuperscript{33,28} Although this is a travesty, it serves as a wake-up call. American Psychiatric Association chief executive officer and medical director Saul Levin, MD, MPA, stated: “It is time that the FDA [Food and Drug Administration] convene an expert group of minority experts to create a road map of implantable steps to address the illnesses in which health inequity has exponentially increased morbidity and mortality in underrepresented minorities.”\textsuperscript{34,35}

The death of Jamaican-born physician Susan Moore, MD, gained national attention. Moore died of COVID-19 related complications 2 weeks after posting a video on social media on December 4, 2020.\textsuperscript{36,37} She wrote that her physician dismissed her complaints, made her feel like a drug addict, and conveyed that he did not respect her as a fellow physician.\textsuperscript{36,37}

Moore’s experience made me reflect on my own when I was hospitalized for COVID-19. As a Puerto Rican and cisgender gay male psychiatrist, I am blessed to live, receive medical care, and practice psychiatry in one of the most liberal and ethnically diverse cities in the world: New York City. I was lucky that the team who treated me was ethnically diverse.

Most of my patients are African American and Latino, who are in the low socioeconomic status bracket. Many underrepresented minorities often are working in jobs that are not amenable to teleworking, and they...
use public transportation that puts them at risk for exposure to COVID-19. Several of my patients have lost their jobs or have been offered fewer hours. The financial strain that this causes has had negative impacts on my patients’ mental health. This pandemic has brought to light the inequity in health care ser-

vices minorities receive throughout the United States. It serves as an opportunity for the medical and psychiatric community to better address the needs of this patient population, while maintaining appropriate safety precautions and public health measures.

Missed Opportunities, Family, and Travel
Throughout the year, we were asked to avoid family gatherings, holiday functions, and unnecessary travel. Leisure escape time was no longer safe. Public health officials, including Anthony Fauci, MD, pleaded with Americans to stay home and only socialize with their pods. Unfortunately, time and again, Americans did not listen. We saw spikes in cases, hospitalizations, and deaths after each of the summer holidays and even more so after Thanksgiving and Christmas. According to the New York Times, the daily death toll for the US during the second wave of COVID-19 started to pick up in early November and has been steadily increasing since then.

On the other hand, some Americans did listen, and many stayed home. The year 2020 was not the year to travel. For the safety of our elderly and immunocompromised friends and family, we had to embrace creative ways to “see” each other. The COVID-19 pandemic forced us to embrace virtual communication in almost every aspect of our lives—from how we work, receive, and give our medical care, and connect with loved ones. It is not everything. It is not the same. But it is the hand the world was dealt. It is en-

deaths from a single catastrophe. Over half are in the US during the second wave of COVID-19 started to pick up in early November and has been steadily increasing since then.

The Next Chapter
It has been 1 year since COVID-19 turned our world upside down. The COVID-19 outbreak will eventually end, but public health experts expect this will not be the last pandemic. Will we have learned the right lessons so we can more successfully weather the next one?

Dr Tirado is a forensic psychiatrist at Lincoln Medical Center in the Bronx, New York, and assistant clinical professor of psychiatry at Weill Cornell Medicine, New York, New York. The author reports no conflicts of interest concerning the subject matter of this article.

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Since at least 1962, when the FDA first grappled with the conundrum of who should get access to the novel dialysis machine, health care professionals, bioethicists, and public health leaders have wrestled with how to justly distribute the angel of life-saving resources when the devil is in the details precisely because the resource is scarce. Sadly, not everyone who needs and could benefit from life-saving care can receive it. Allocation decisions for COVID-19 vaccines are especially weighty, given that the virus has thwarted most other therapeutics, besieged the health care system, collapsed the economy, and caused widespread social disruption.

**Resource Allocation**

There are many vexing ethical issues surrounding COVID-19 vaccine allocation. Fortunately, we are not alone in navigating this moral labyrinth. In the past few months, several of the most respected public health institutions in the world have published reports that provide ethical frameworks for allocating the COVID-19 vaccine (Table 1-3,5,6). Any ethical framework must consider those with serious mental illness, and the hundreds of members of our specialty who are on the front line delivering COVID-19 care. (Note: future Psychiatric Times articles will consider exactly where individuals with mental health illness should fall in the vaccine prioritization queue.)

Several observations about the ethics of COVID-19 vaccine allocation in the United States can be drawn from these summaries. First, the 3 American frameworks summarized in the Table contain principles of distributive and procedural justice. In the context of allocating scarce resources, “distributive justice” concerns the outcomes that are sought when competing ethical values, principles, and interests must be balanced. For example, ethical vaccine prioritization must balance utility in maximizing the reduction of severe disease and mortality from COVID-19, ensuring groups with health disparities have fair access to the vaccine and promoting respect for the dignity of vulnerable populations, such as those with disabilities.

Procedural justice” concerns the process of specifying and weighing these many values, principles, and interests. For vaccine allocation planning and execution, an ethical process requires wide stakeholder input, transparent decision-making, and a clear mechanism for adjusting criteria in response to new scientific data and logistic developments.

The Table also illustrates the critical difference between the clinical ethics most of us practice, in which the preferences and needs of the individual patient are the locus of decision-making, and public health ethics, in which the common good is the focus. Another key distinction between the clinical and public health ethics is that legal, social, and even political factors wield much more powerful and pervasive influence in public health deliberations. The distinguishing pathophysiology and unique epidemiology of the COVID-19 crisis, stressing the nation at one of the most divisive times in US history, has revealed as never before the fault lines in American health care. The legacy of health disparities and structural racism have enabled the COVID-19 pandemic to savagely afflict communities of color.7 This made it morally incumbent upon the export multidisciplinary panels who crafted these frameworks to incorporate not only

### Table. Ethical Frameworks for Vaccine Allocation1-3, 5,6

<table>
<thead>
<tr>
<th>Institute</th>
<th>Ethical principles</th>
<th>Initial prioritization</th>
</tr>
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</table>
| The National Academy of Sciences, Engineering, and Medicine5 | Maximum benefit  
- Protect public health  
- Promote socioeconomic well-being | Phase 1a  
- High-risk health workers  
- First responders |
|                                               | Equal concern  
- Treat every individual as having equal dignity, worth and value | Phase 1b  
- Any adult with comorbid conditions that place them at significantly higher risk  
- Older adults living in congregate or overcrowded settings |
|                                               | Mitigation of health inequities  
- Address populations with heaviest burden of COVID-19 due to health disparities | Phase 2  
- K-12 teachers, staff childcare workers  
- Essential workers in industries critical to social function who are at higher risk of exposure  
- Individuals of all ages at moderate risk due to comorbidities  
- Individuals in homeless shelters, group homes, with disabilities, including serious mental illness, and staff  
- Individuals in prisons, jails, and staff  
- All older adults not included in phase 1 |
|                                               | Fairness  
- Engage those most affected by COVID-19  
- Make impartial allocation decisions and apply criteria fairly | Phase 1c  
- Individuals 65 to 74 years old  
- Individuals 16 to 64 years old with high-risk medical conditions  
- Essential workers not included in phase 1b |
|                                               | Transparency  
- Communicate to public openly, clearly, accurately about all aspects of framework allocation |                                                                                      |
|                                               | Evidence-based  
- Base entirety of framework on the best available and constantly updated scientific information and data |                                                                                      |

| Advisory Committee on Immunization Practices1-3 | Phase 1a  
- Health care personnel  
- Residents of long-term care facilities |                                                                                      |
|                                                 | Phase 1b  
- Individuals 75 years or older  
- Frontline essential workers |                                                                                      |
|                                                 | Phase 1c  
- Individuals 65 to 74 years old  
- Individuals 16 to 64 years old with high-risk medical conditions  
- Essential workers not included in phase 1b |                                                                                      |

| Johns Hopkins Center for Health Security1 | Promoting common good  
- Promote public health  
- Enable social and economic activity | Tier 1  
- Those most essential in sustaining ongoing COVID-19 response  
- Those at greatest risk of severe illness and death, and their caregivers  
- Those most essential to maintaining core societal functions |
|                                           | Treat individuals fairly and promote social equity  
- Address racial/ethnic disparities in COVID-19 mortality  
- Recognize contributions of essential workers previously overlooked | Tier 2  
- Those involved in broader health provision  
- Those who face greater barriers to accessing care if they become seriously ill  
- Those contributing to maintenance of core social functions  
- Those whose living or working conditions place them at elevated risk of infection even if their risk of severe illness and death is lower |
|                                           | Promotion of legitimacy, trust, and ownership  
- Respect diversity of values and beliefs of pluralistic society  
- Make decisions that are clear, understandable, open for review |                                                                                      |
|                                           | Promote public participation in creation and review of decision processes |                                                                                      |
A Fragile Consensus

For ethical guidance to be flexible enough to respond to the rapidly evolving scientific knowledge and dynamic nature of conditions on the ground, it cannot be overly prescriptive or rigid. This leaves latitude for interpretation, especially among the states where the actual implementation occurs and, hence, room for disagreement, especially as we move down the levels of the framework. A clear example of this phenomenon was when the federal government encouraged states to begin vaccinating all those 65 years and older. But when the nationwide immunization effort lagged the schedule, the Department of Health & Human Services modified prior US Centers for Disease Control and Prevention guidance, ruling that 75 years of age should be the cutoff for 1b vaccine prioritization.

Among the most problematic questions is “Who is an essential worker?” For a single mother, it is essential that her school-age child’s teacher be vaccinated so schools can open, so the mom can return to work. On the other hand, mass transit and social services workers may be necessary for survival for an urban family whose breadwinner has lost their job due to the pandemic. Even reasoned efforts to choose the most crucial groups raise the specter of social worth criteria, by which some individuals are deemed more valuable than others.

The Neglected Cohort

A careful review of these frameworks suggests that they overlook patients with mental illness and mental health care professionals. Patients with mental illness and those who care for them are often sidelined during major health care initiatives; that other struggle for parity and equity extends to vaccine allocation in this pandemic.

Mental health has been discounted in a range of health care scenarios, from representation on the expert panels that produced the reports to inclusion of psychiatrists in essential health care worker categories to specific attention to the needs and challenges of vaccinating patients with mental illness. An ethical analysis of how our profession and patients should fit into vaccine allocation frameworks, and practical recommendations for promoting immunity in our community, remain to be done.

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PHOTOGRAPHY:JOHNMcDIARMID/CORBIS
This Special Report contains articles about cannabis use and its potential complications, including cannabis use disorder (CUD). The first piece highlights the use of cannabinoids among the geriatric population. Cannabis and cannabidiol (CBD) use in older adults has become more prevalent as a result of reduced stigma; leniency in state restrictions on possession and sale; and advertisements touting benefits for chronic pain, peripheral neuropathy, stress, anxiety, depression, insomnia, headaches, and the adverse effects of chemotherapy. Medical marijuana use by individuals 65 and older has increased more than 8-fold in recent years. The article nicely summarizes how heavy marijuana use can cause mild functional and structural brain impairments, affecting attention, processing speed, motor coordination, verbal memory, and executive function. Overall, every older patient, along with their caregivers, should be queried as to their use of cannabis products. They should also be cautioned that those with preexisting neurocognitive impairment, such as Alzheimer disease, might be particularly vulnerable to adverse effects such as drowsiness, dizziness, fatigue, and mood changes.

We have a changing cultural ethos regarding cannabis acceptability; nevertheless, many users will suffer from its use. Some will develop CUD, and many can damage their educational achievement, work lives, health, and relationships. The next article in this Special Report includes an overview of clinical insights about the increasing number of cannabis users who experience negative effects, ranging from the annoying to the catastrophic. As noted, these effects arise from 3 sources: potential users’ sharply decreased perception of risk in recent years, easy availability of cannabis, and increased potency of Δ9-tetrahydrocannabinol (THC) in legal and illegal cannabis sources. In recent years, THC concentrations in smoked cannabis doubled to 17.1% in 2017. Due to these high THC concentrations, clinicians need to recognize psychiatric complications of heavy repeated cannabis use, such as depression, anxiety, psychosis and, although rare, the cannabinoid hyperemesis syndrome.

Furthermore, although subtle compared with alcohol or opioid withdrawal, cannabis withdrawal does occur and includes irritability, anxiety, depression, insomnia, disturbing dreams, anorexia, abdominal pain, tremors, sweating, fever, chills, headache, and craving. Off-label use of medications for withdrawal are suggested and might include gabapentin and the THC analogue dronabinol, and limited amounts of benzodiazepines to relieve anxiety and insomnia. However, there has been little efficacy in the treatment of CUD.

The final article focuses on patients with schizophrenia. It synthesizes the large literature on cannabis and psychosis risk. The piece also reviews the literature on genetic associations, earlier age of onset, poorer treatment outcomes, and cognition. For example, a critical meta-analysis found an association between better cognitive performance and cannabis use in schizophrenia, a finding that merits careful replication because another analysis of first-episode schizophrenia found patients with psychosis and current cannabis use had significantly lower premorbid and current IQ scores.

We hope that you find that this educational Special Report enhances your understanding of the rapidly changing field of cannabinoids and their clinical implications, particularly for our geriatric population and patients with schizophrenia.

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The Age of Cannabis Has Arrived: Issues for Older Adults

Marc Agronin, MD

A new question must be added to the list that mental health clinicians ask their older patients while taking a history, regardless of age: “Have you used any cannabis products recently?”

I learned this lesson during a follow-up appointment with an 82-year-old man with Alzheimer disease. He reported some rather abrupt cognitive decline, and I asked him and his wife about recent medical changes without finding any clear precipitant. Finally, his wife sheepishly confessed that their son had sent them a grab bag of cannabis-derived products that the patient was taking. The family was desperate for anything to help his cognitive decline and they had heard that cannabis was a miracle cure for Alzheimer disease and many other conditions. Unfortunately, the patient received no benefit but did experience some mild, noticeable adverse effects. Without my probing, I never would have known. The next patient I asked explicitly about using cannabis products responded in an equally explicit manner: “No I haven’t,” he said, “but can you get me some?” It was clear that the age of cannabis had arrived.

Older individuals with psychiatric disorders are increasingly using cannabis, largely in the form of prescribed medical marijuana and cannabidiol (CBD). This trend has been driven by several factors: reduced stigma, lifted restrictions on possession and sale by most states, and the enormous proliferation of articles and ads that tout supposed benefits of cannabis for many conditions that afflict the elderly, including chronic pain, peripheral neuropathy, stress, anxiety, depression, insomnia, headaches, and the adverse effects of chemotherapy.

As a result, medical marijuana use by individuals 65 or older has increased more than 8-fold in recent years, from less than 0.5% in 2006 to 4.2% in 2018 (Figure). In a survey of 345 adults in Colorado, 16% had used medical marijuana since legalization, with half the users being 75 or older. CBD has seen a particularly enormous surge in interest and availability after it was exempted from federal regulation in the 2018 US Farm Bill. Since then, it is estimated that 6.4% of adults aged 45 to 55 and 3.7% of those 55 or older have used CBD at least once.

Cannabis, Cognition, and Quality of Life

Although the cannabis sativa plant contains hundreds of chemicals known as cannabinoids, the 2 main active chemicals are Δ9-tetrahydrocannabinol (THC) and CBD. THC has both psychotropic and euphoric properties and confers the high associated with marijuana, while CBD is noneuphoric because it does not activate the cannabinoid 1 receptor like THC does. The same plants that produce THC also produce CBD. Both THC and CBD come in a variety of forms; they can be smoked, vaporized, eaten, ingested as liquids, used as oils, and applied via creams and cosmetics.

The psychotropic effects of both THC and CBD are mainly because of their interaction with endogenous cannabinoid receptors in the brain, as well as activation of a variety of other cannabinoid and noncannabinoid receptors (ie, serotonergic, glutamatergic, μ-opioid, and η1-adrenergic) in the central nervous system and on immunologic cells. Based on their known and theorized properties, marijuana and CBD have been proposed as remedies to modulate symptoms of stress, insomnia, pain, inflammation, and cognitive impairment, particularly in older individuals. As a result, there are many unsubstantiated claims that THC and/or CBD can treat Alzheimer disease, Parkinson disease, schizophrenia, and anxiety and mood disorders.

Several small case series have suggested a tentative basis for some of these claims. For example, a study looked at the use of an oral spray containing THC and CBD for peripheral nerve pain and found that it was well tolerated and showed a trend toward improvement in pain and sleep. Medical marijuana use has been associated with some improvement in both movements and neuropsychiatric symptoms in individuals with Parkinson disease. One small case series found improvement in behavioral and psychological symptoms of dementia from cannabis oil containing THC.

A related randomized control trial of 50 individuals with dementia and associated neuropsychiatric symptoms did not see any benefit from THC, but did find it was well tolerated and with no appreciable effect on memory. Despite these limited data, agitation associated with dementia is a qualifying condition for medical marijuana in several states.

Gruber and colleagues studied a sample of middle-aged individuals using medical marijuana over 3 months and found improvements in executive function and reductions in depression, insomnia, and impulsivity. They also saw a reduction in the use of benzodiazepines and opioids as well as a normalization of brain activation waves to states seen in normal controls. It is not clear, however, if these neurocognitive results were the direct result of the medical marijuana or an indirect benefit of decreases in pain, anxiety, and insomnia.

Although there are many other in vivo, in vitro, and animal studies of THC and CBD, it is clear that evidence is limited, and there are few randomized controlled trials to support most of their theorized clinical benefits. In addition, these studies are based on a variety of cannabis products from multiple sources and with variable contents. The 2 exceptions include a Food and Drug Administration (FDA)-approved form of synthetic THC known as dronabinol, which is used for treating appetite and weight loss resulting from AIDS as well as nausea and vomiting from chemotherapy, and a medication containing CBD for the treatment of 2 rare childhood seizure disorders. Dronabinol has also been studied in Alzheimer disease to treat anorexia and agitation and was found to be well tolerated with variable efficacy for both conditions. In the European Union, nabiximols, a CBD-THC combination, has been approved for the treatment of muscle spasms associated with multiple sclerosis.

The Downside of Cannabis Use

The use of medical marijuana and CBD in older adults must be approached with caution because there are several potential adverse effects.

It has been well established that heavy marijuana use in both young and middle-aged adults can cause mild functional and structural brain impairments affecting attention, processing speed, motor coordination, verbal memory, and executive function. Although these effects may be more variable with lighter use in

[Image 20x20 to 796x628]
older adults, they may be amplified by preexisting brain impairment as well as by underlying pulmonary and cardiovascular conditions, especially when medical marijuana is smoked or vaped.46 One review of 184 older patients (median age, 82) who were on medical marijuana for 6 months found that approximately 80% reported some benefit for the treated symptoms, but one-third reported adverse effects, including dizziness (12%) and sleepiness and fatigue (11%).13 Other reported adverse effects from a national epidemiologic survey included changes in mood and cognition, psychosis, increased heart rate and blood pressure, urinary retention, and blurred vision.14 In addition, THC has been associated with impaired driving in young adults, which could also be a problem in older drivers who may be impaired at baseline.15

A meta-analysis of CBD use found that it is generally well tolerated with few adverse effects, the most common one being diarrhea.16 One review of 184 older patients, including blood thinners, antidepressants, and antipsychotics.17 Older patients, including blood thinners, antidepressants, and antipsychotics.17

What To Ask Patients, and What To Tell Them
In this new era of medical marijuana and CBD, there are several important takeaways for clinicians working with older patients. Do not assume that because a patient is elderly and has physical or cognitive limitations that they do not fit the profile of a cannabis user. To the contrary: Every older patient along with their caregivers should be queried as to their use of cannabis, whether recreational, socially, or with medical purpose. The new evidence indicates that the use of pharmaceuticals, including blood thinners, antidepressants, and antipsychotics, poses many potential risks. Concomitant medical conditions must be reviewed for potential vulnerabilities, such as an individual with hypertension using a product that increases blood pressure or heart rate, or an individual with chronic obstructive pulmonary disease using vaping oils. Potential drug-drug interactions also need to be considered, with a focus on the categories of medications discussed in the article. Patients and their caregivers need to understand that nearly all benefit claims are largely unsubstantiated, as they lack a rigorous scientific basis. Slick articles and ads generally exaggerate potential benefits, or they refer to in vitro or animal studies and anecdotal reports, making them sound as if they constitute direct evidence of clinical effects. They also need to understand the differences between THC and CBD, along with the fact that production is largely unregulated, so products can have many different ingredients and properties. Several studies have found wide discrepancies between labels for cannabis products and their actual contents, especially when it comes to the amount of THC or CBD.7 Thus, many products that claim only to have CBD actually have varying degrees of THC present. This lack of consistency often accounts for both inconsistent clinical effects as well as adverse effect issues, and these factors lead many older adults to discontinue use of cannabis products.

Finally, keep in mind that older patients with preexisting neurocognitive impairment such as in Alzheimer disease might be particularly vulnerable to adverse effects such as drowsiness, dizziness, fatigue, and mood changes, which in turn can account for significant and unpredictable fluctuations in cognition and behavior. Such unpredictability (in the amount of drug being ingested over time and the ensuing effects on brain and body) is exactly the sort of variability that can be hazardous in the older patient. Compounding these risks is the fact that many individuals will use products such as CBD oil without the knowledge and supervision of a knowledgeable clinician. The bottom line is that more rigorous scientific study using randomized controlled trials is needed to substantiate the proposed benefits of cannabis and more fully understand the range and impact of common adverse effects.

Dr Agronin is the chief medical officer at MIND Institute at Miami Jewish Health.

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Cannabis 2021
What Clinicians Need to Know

Laurence M. Westreich, MD

Lost in the various public policy arguments fueling cannabis decriminalization and legalization laws across the United States is the fact that a percentage of individuals who use cannabis will experience negative effects, ranging from bothersome to the catastrophic. These difficulties arise from a sharply decreasing perception of risk, easy availability of the drug, and increased potency of Δ-9-tetrahydrocannabinol (THC) preparations. The arithmetic of cannabis remains immutable: Best estimates are that about 9% of individuals who use cannabis will become dependent on the substance at some point in their life,1 and if the number of those who use cannabis goes up, the total number of those experiencing problems with the substance will rise also. Clinicians must learn to manage cannabis-related problems in this growing population.

The acute and chronic problems cannabis-dependent individuals face are serious, disheartening, and deserving of treatment. National Survey on Drug Use and Health (NSDUH) data on 505,796 Americans2 show that between 2008 and 2016 individuals aged 12 to 17, who met criteria for a cannabis use disorder (CUD), were 25% more common in states that had enacted Recreational marijuana laws (RMLs) as opposed to those who did not. In addition, the THC content of the various preparations of cannabis has risen over the past 10 years. Studies show that the mean THC concentration in smokable marijuana increased from 8.9% in 2008 to 17.1% in 2017,3 and half of those who frequently use marijuana ingest concentrations of at least 80% THC.4 In 2014, THC concentrate in Colorado had an average THC percentage of 56.6%, while by 2017 the average was 68.6%, with some retail stores cheerfully advertising a 95% THC rate in their products.7

Cannabis-related problems, like lack of motivation, usually become apparent after many years of use. Given cannabis’ pharmacological designation as a sedative-hypnotic substance, it is hardly surprising that common complaints on presentation to treatment include acute intoxication with high-potency edible THC preparations6; psychiatric phenomena such as depression, anxiety, and psychosis5; and cannabinoid hyperemesis syndrome (CHS).8

Clinicians should at least consider their patients’ cannabis use as a precipitating or exacerbating factor in any psychiatric or medical syndrome. Also, although the DSM-55 contains a useful list of cannabis-related signs and symptoms, many individuals with cannabis-related problems do not meet the full criteria for CUD. For instance, while the casual cannabis smoker may present with a depressive picture but meet no other criteria for CUD, cessation of cannabis use may be necessary to achieve resolution of the patient’s dysphoria, anhedonia, and fatigue. CHS, cyclic episodes of nausea and vomiting often relieved with hot baths, can be a confusing emergency department presentation. Other medical presentations of heavy cannabis smoking include cough, bronchitis, lung hyperinflation,9 as well as acute lung injury from vaping.10 Legal11 or employment12 concerns related to cannabis may also generate first visits with a clinician.

As shown in Table 1, the DSM-5 criteria list the myriad problems that can arise from cannabis use. To fulfill criteria for CUD, the patient must demonstrate at least a yearlong “problematic pattern of cannabis use” and meet at least 2 of the criteria. However, the clinician would do well to consider any cannabis-related problem as a possible contributor to the patient’s reason for presentation.

The patient should be offered a coherent psychotherapy aimed at first minimizing the harms of cannabis use, and then achieving abstinence from the substance. Treatment of any co-occurring psychiatric conditions should be initiated concurrently with the below strategies, focused on cannabis cessation. Manualized techniques like cognitive behavioral therapy,14 motivational enhancement therapy,15 and contingency management16 have shown measurable, if modest, improvements in outcome criteria such as frequency of cannabis use, number of dependence symptoms, quantity of cannabis use, and negative consequences of cannabis use. These effective treatments share a good understanding of the addictive process, practical and easily deployed interventions, and a focus on small gains. Most clinicians use a mix of therapeutic techniques, which often include cannabis-specific interventions (Table 2).17,18

Peer-led support groups like Alcoholics Anonymous, although commonly recommended as an adjunct to the treatment of substance use disorders, should be carefully selected if recommended for the individual who uses cannabis. Members of peer support groups can be wrongly dismissive of those who only use cannabis. If possible, clinicians should recommend groups like Marijuana Anonymous,19 or specific groups which are known to understand the seriousness of CUD. Similarly, impatient treatment or intensive outpatient programs should be carefully selected for their focus on or at least understanding of CUD.

A common—and counterproductive—fallacy about cannabis is that the substance does not cause withdrawal. In fact, the withdrawal syndrome from cannabis, though unlikely to cause serious medical problems, is uncomfortable and a leading reason that individuals who use cannabis do not stop their use of the substance. Withdrawal therefore requires treatment. Common phenomena associated with cannabis withdrawal include irritability, anxiety, depression, insomnia, disturbing dreams, anorexia, abdominal pain, tremors, sweating, fever, chills, headache,12 and craving.19

A powerful first step in engaging the patient in treatment to beat their dependence on the drug is the clinician’s acknowledgement of the withdrawal syndrome and offer to find symptomatic relief. Patients should remain well-hydrated, eat a healthy diet, and exercise regularly during the withdrawal period. Although no medications have been approved by the US Food and Drug Administration (FDA) to treat cannabis withdrawal, symptom-relief medications like gabapentin20 and the THC analogue dronabinol21 can be prescribed. Judicious use of benzodiazepines to relieve anxiety and insomnia is indicated in some cases.

Treatment of cooccurring psychiatric illnesses with the appropriate medications is vital to the treatment of CUD. Although no medications have FDA-approved indications for the specific treatment of CUD, 2 have shown suggestive data in studies, and can be prescribed for patients needing additional pharmacological support. In small studies, the anticonvulsant topiramate22 demonstrated improved retention in treatment over placebo and gabapentin23 showed better treatment retention and a decrease in cannabis use and depressive symptoms. Various trials of dronabinol and nabulone,
both THC analogues; nabiximols, a combination of THC and CBD; and N-acetylcysteine, a glutamatergic modulating dietary supplement, have shown little efficacy in the treatment of CUD.12

Individuals who use cannabis may question any need for addressing their use by noting the ongoing success of cannabis legalization in the US, cannabis’ lack of lethality (as compared to opioids), and the national provenance of the smokable varieties of cannabis. Clinicians should focus instead on the clinical issues that have brought the individual to treatment. Has the drug contributed to problems at work or school? Is there a psychiatric condition or substance, be realistic about the effects of cannabis, and encourage the path for reducing or stopping its use.

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Diagnosis is Key

ADHD is the most common presenting neurobehavioral disorder that pediatricians and child psychiatrists will see in their course of practice and is second only to asthma when ranked among all chronic pediatric illnesses, Wilens explained as he opened the discussion. The prevalence of ADHD among children is between 6% to 9%, regardless of country of origin.

Diagnosis can be made as young as age 4. Behavioral interventions are the first-line treatment option. When deemed appropriate and necessary, stimulant medications are the first-line choice for pharmacotherapy, according to the 2019 American Academy of Pediatrics guidelines for the care of ADHD.

A key challenge associated with ADHD is making an accurate diagnosis, Robert L. Findling, MD, MBA said, noting that a countless number of things may make a child appear inattentive or fidgety.

“[Diagnosis] can only be done by a careful assessment, both cross-sectionally and over time, [and] pediatricians are particularly well-equipped to do such a thing because [they] have the benefit of watching children grow up,” Findling explained. He added that comorbidities, such as oppositional defiant disorder, anxiety, depression, and bipolarity, are the rule and not the exception in the setting of ADHD. These can complicate the clinical picture and, when left undiagnosed or untreated, can mask the benefits from ADHD medication. “You have to know the whole child,” he said. “There are many things … that will not respond to ADHD treatment.”

Approximately 70% to 75% of kids with ADHD have a comorbid medical or psychiatric disorder or coexisting psychosocial or environmental problems, Harlan R. Gephart, MD added. “Autistic spectrum disorder, family issues, divorce, [a] parent’s separation, [the] death of a parent … [can] look like ADHD [and] would give you a positive Vanderbilt Rating Scale for ADHD,” he said. “[They can] make you inattentive and distractable. That all has to be sorted out.”

To help manage ADHD, pediatricians and child psychiatrists would benefit through collaboration, Findling said. “Sometimes it just takes a bunch of people working together, putting the kid right in the center,” he explained.

However, Mark Wolraich, MD explained that communication between all players remains an issue. Information asymmetry between parents, schools, pediatricians, child psychiatrists, and therapists is common in ADHD management. “Some [of these barriers] are there for protection of health information, but they [can] really decrease the communication,” he said.

ADHD Management During the COVID-19 Pandemic

In addition to these challenges, the panelists discussed several downstream consequences of the COVID-19 pandemic and ADHD management; some of them have been positive, others have not.

Telemedicine

For years, telemedicine was not a reimbursable intervention for physicians, Wolraich pointed out. However, that changed during the pandemic when delivery of goods and services shifted to a more contactless approach. Telemedicine, Wolraich noted, is beneficial for ADHD management because it allows for better observation of the child in their more natural home environment and is more conducive to the shorter follow-up intervals required during rapid dose titration of ADHD medication.
“Patients can come to appointments much easier,” Wilens said. “[Parents] don’t have to drive far distances, [they] don’t have to take off a half day of work, kids don’t have to miss sports [or] school. Our no-show rates [have] dropped precipitously.”

In addition, as ADHD stimulant medications are scheduled drugs, Wilens also observed that the relaxing of regulatory oversight during the pandemic for prescribing controlled substances via telehealth visit has proven helpful.

The downside of increased telemedicine include access to adequate internet bandwidth, technical glitches, and a loss of in-person human connection, the panelists noted.

**Virtual Schooling**

Another challenge associated with a more virtual world in the wake of the COVID-19 pandemic, is not all children are back in-person learning at schools. This can be problematic for patients with ADHD, the panelists noted. “For many kids and families, it’s an absolute disaster,” Ann Childress, MD said. “[Kids with ADHD] can’t sit [still] in front of the camera … they are getting in trouble … they can’t figure out what link they’re supposed to [click on for] the next class … they’re running around the house.” Parents fear their kids are falling behind and are considering quitting their jobs until in-person school resumes, she added.

But it’s not just concerns over learning, children with ADHD have strengths that can’t be observed virtually, Findling said. “[So] now they have lost the chance to succeed in domains that they might have been successful at when [school] was in person and not via screen,” he explained.

**Medication Access**

COVID-19 has also made for supply chain issues that have created access barriers for stimulant medications. “We’re dealing with distribution problems, [and] people are having more problems finding stimulants … they may have to go to 3 or 4 different pharmacies,” Wilens said.

Because pharmacies will not always tell someone over the phone if they have a particular stimulant medication in stock over robbery concerns, a parent may drive there only to learn the medication isn’t available. “Then I have to … go back and send [the e-script] to another pharmacy, [and] it takes up a lot of time just to try and get somebody their medicine,” Childress said. Unfortunately, COVID-19 has forced many people out of work and that has also meant lost of health insurance for families, making it difficult to afford brand-name ADHD medications that they have already been taking. “I’m having to do things that I don’t like to do, and that’s switch people to immediate-release [agents] that they can afford,” Childress said.

Using the drug differently than was prescribed or using the drug without a prescription—has now outpaced opioid [use] among teens and young adults, Wilens explained, with the highest rates of abuse aggregating at colleges and universities.

“[It’s] really exciting to hear that we have new potential alternatives [for use in ADHD] … and that[ ] they are trying to make them safer,” Wilens said.

Several stimulant drugs in development may also help control medication abuse because they are being made with manipulation-resistant technology, Childress explained. “There are about 40 drugs in the pipeline in various places,” she said. For instance, one product is a capsule containing crush-resistant pellets of an immediate-release amphetamine. The difficulty of grinding the pellets down into a powder for snorting prevents misuse intranasally. Other products in development use prodrugs which must undergo conversion in the gastrointestinal tract before becoming active. Nonstimulant drugs currently being investigated for use in ADHD have mechanisms similar to antidepressants.

To watch the complete custom video program, visit psychiatrictimes.com/viewpoints/
Adult-Onset ADHD Raises Questions

Chris Aiken, MD

For our recent studies may have turned what we know about attention-deficit/hyperactivity disorder (ADHD) on its head. By following large cohorts from early childhood to adulthood, they claim to have discovered that ADHD can start in adults who did not have the disorder before the DSM-5 cutoff of 12 years. However, before we rewrite the DSM and start prescribing stimulants to every adult who cannot concentrate, it is important to take a closer look at this research.

In 3 of the 4 papers, the adult-onset ADHD actually began in the teenage years. Furthermore, many of these teenaged-onset cases (29% to 75%) had symptoms of ADHD in their childhood that were either below the threshold for the full diagnosis or were classified as part of a related disorder (eg, conduct disorder or oppositional-defiant disorder).

The fourth paper claimed to identify new-onset ADHD in middle-aged adults, and it made the biggest headlines. The study followed a group of more than 1000 residents of New Zealand from age 3 to 38 years as part of a larger investigation on the effects of adverse birth experiences on health. Researchers gathered symptoms of ADHD at 3 time points: ages 5 to 7; 11 to 15; and finally at age 38. What they discovered surprised them. Most of the children with ADHD no longer had the full disorder as adults, and most of the adults who met criteria for ADHD in middle age did not have the full disorder in childhood. The problem with this surprise discovery is that they did not ask the participants when their ADHD symptoms began, so these may have been teenaged-onset cases like we saw in the 3 other studies.

Comorbid Confounders and Other Confusions

The New Zealand study counted 27 adults with ADHD who did not have the full disorder in their childhood. A quick breakdown of those cases suggests that other disorders could have caused the attention problems endorsed by these patients. Specifically, 10 patients had conduct disorder in childhood; 15 had substance use disorders as adults; and 15 sought treatment for major psychiatric disorders as adults.

Two other studies that looked at purported cases of adult-onset ADHD concluded that the majority (93% to 95%) of the cases were better explained by sleep disorders, substance use disorders, or another psychiatric disorder.

If adult-onset ADHD does exist, it may not be the same disorder as childhood-onset ADHD. Indeed, most cases of adult-onset ADHD can be better explained as true ADHD that was partially expressed in childhood; false positives in patients whose symptoms are due to another disorder; or false positives in healthy people who overendorsed their symptoms during the diagnostic interview.

But what if there remains a small number of individuals whose ADHD genuinely begins in adulthood? These studies point to that possibility, but they do not tell us whether these cases share common biological markers, familial patterns, and treatment response with childhood-onset ADHD. The gender distribution, for example, was different, with more males in the childhood-onset cases.

False Positives and Negatives

When someone goes through the effort to see a psychiatrist, there is a good chance that they have a real psychiatric problem. Or, as Groucho Marx put it, “Anyone who goes to a psychiatrist ought to have their head examined.” With community samples, the working assumption is that the participants are “normal,” which is why this kind of research is so prone to false positives. The false positives in these community studies were further elevated by the reliance on self-report.

Although these studies attempted to rule out other causes of adult-onset ADHD, those exclusions are hampered by false-negative rates. For example, it is not unusual for patients to forget past episodes of mania or psychosis, and those episodes often cause long-standing cognitive problems that could be mistaken for ADHD. Some important causes, like autism spectrum or personality disorders, were not evaluated in these studies.

Before we rewrite the DSM and start prescribing stimulants to every adult who cannot concentrate, it is important to take a closer look at this research.

REFERENCES

First recognized in 1872 by George Huntington, MD, Huntington disease (HD) is a neurodegenerative disorder that is characterized by progressive decline in motor functioning, cognition, and behaviors. In North America, approximately 30,000 individuals have this illness, and an additional 150,000 individuals are at risk for developing it. HD tends to occur more commonly among individuals of European descent, with a prevalence rate of 10 to 15 per 100,000. The incidence of HD is approximately 4.7 to 6.9 new cases per million per year in the Western population. The median age of diagnosis for HD is approximately 40 years. It is rare for HD to be diagnosed among individuals 20 years or younger, or among individuals 65 years or older. HD affects men and women equally.

**Neuropathology of HD**

The neuropathological hallmark among individuals with HD is the progressive atrophy of caudate nucleus and putamen due to neuronal loss. The clinical features of HD occur due to the loss of medium-sized projection spiny neurons in the dorsal striatum, which express the dopaminergic type 1 or 2 receptors. As the illness progresses, global neuronal loss and generalized cerebral atrophy occur, and the overall brain weight can decrease by up to 40%. These medium-sized projection spiny neurons use the inhibitory transmitter γ-aminobutyric acid and either dynorphin, enkephalin, or substance P as cotransmitters. It is thought that the loss of inhibitory input from the medium-sized spiny neurons, which usually exert an inhibitory effect, is the reason for the uncontrolled movements characteristic of individuals with HD. Individuals with HD also have intranuclear inclusions and protein aggregates in the dystrophic neurons of both the striatum and cortex. Additionally, the number of cortical inclusions correlates directly with the length of the CAG repeat expansion and the age of onset of the illness. Furthermore, these intranuclear inclusions tend to appear before the loss in brain weight. The loss of brain weight precedes the loss of body weight and the onset of neurological symptoms.

**Table 1. Treatments for Motor Symptoms**

- **Vesicular monoamine transporter type 2 inhibitor**
  - Tetrabenazine
  - Deutetabenazine
  - Depression, drowsiness, anxiety, parkinsonism, fatigue, akathisia, gastrointestinal distress, neuroleptic malignant syndrome (rare)
  - Adverse effects are dose-related
  - Boxed warning for use among individuals who are actively suicidal or have inadequately treated depression

- **Dopamine receptor blockers**
  - Typical antipsychotics (haloperidol, pimozide, fluphenazine, tiapride)
  - Atypical antipsychotics (olanzapine, quetiapine, risperidone)
  - Weight gain, drowsiness, parkinsonism, tardive dyskinesia, akathisia, hyperprolactinemia, neuroleptic malignant syndrome
  - Same as above plus metabolic effects

- **Glutamate release inhibitor**
  - Riluzole
  - Depression, diarrhea, nausea, headache, fatigue

- **Noncompetitive N-methyl-D-aspartic acid-type glutamate receptor antagonist**
  - Amantadine
  - Depression, drowsiness, anxiety, parkinsonism, fatigue, akathisia, gastrointestinal distress, psychosis, neuroleptic malignant syndrome (rare)

- **Deep brain stimulation (DBS)**
  - Bilateral globus pallidus interna DBS
  - Decline in ambulation and cognition

**Clinical Features of HD**

There is significant variability in the type, timing, and progression of clinical symptoms. The clinical course can be divided into premanifest and manifest periods. The premanifest period can be further divided into presymptomatic and prodromal periods. During the presymptomatic period, which is approximately 10 to 15 years before the onset of symptoms, individuals are not clinically distinguishable from those individuals without HD. During the prodromal period, individuals present with subtle motor, cognitive, and behavioral symptoms. Once individuals enter the manifest period with prominent motor, cognitive, and behavioral symptoms, the symptoms continue to progress and worsen, and the illness is ultimately fatal. The median survival time from the onset of motor symptoms is approximately 18 years.

The symptoms of HD can be divided into 2 broad categories: progressive motor symptoms and neuropsychiatric symptoms. A diagnosis of HD is made only when the characteristic motor features manifest, even among individuals who are gene positive. The motor symptoms of HD can be divided into 2 main categories: abnormal involuntary movements and impaired voluntary movements. Among individuals with HD, the most common abnormal movements are characteristic of chorea, which is among the early presenting symptoms, especially among individuals with adult-onset HD. Impaired voluntary movements are more common among individuals with earlier-onset HD (younger than 21 years). They are seen among patients with adult-onset HD during the severe stages of the illness. Impaired voluntary movements include motor incoordination, bradykinesia, rigidity, dystonia, gait disturbances, and eye movement abnormalities. Dysarthria and dysphagia are seen in later stages of the illness, often leading to choking and aspiration.

**Manifestations**

Neuropsychiatric symptoms are often present well before the motor symptoms manifest, sometimes decades prior, and include depression, irritability/aggression, executive dysfunction (eg, apathy, obsessive-compulsive behaviors), psychosis, cognitive decline, and dementia.

Individuals with the HD gene who are presymptomatic exhibit a higher prevalence of neuropsychiatric symptoms. Neuropsychiatric complaints are the presenting symptom in approximately half of individuals. Among symptomatic individuals, more than 70% have neuropsychiatric symptoms, with symptoms often waxing and waning. Neuropsychiatric symptoms are often multifactorial in origin and are considered to be the most burdensome symptoms for caregivers and family members.

In a study of 1993 individuals with HD mutations from 15 European countries, 73% of the participants had some neuropsychiatric symptom within the past month. Moderate to severe apathy and depression were seen in 28.1% and 12.7% of the participants, respectively. Similarly, irritable and aggressive symptoms were present in 13.9% of the participants, and 13.2% of the participants showed obsessive/compulsive behaviors (OCDs). However, moderate to severe psychotic symptoms were found in only 1.2% of the participants. Apathy was more prevalent in advanced stages of the disease (11% in early stages vs 54.6% in advanced stages); it may be the only
### Table 2. Treatments for Common Neuropsychiatric Manifestations

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apathy</td>
<td>- Encourage social and physical activities</td>
</tr>
<tr>
<td></td>
<td>- Reduce and/or discontinue medications that may worsen apathy (eg, antipsychotics, tetrabenazine)</td>
</tr>
<tr>
<td></td>
<td>- Treat underlying depression, if present</td>
</tr>
<tr>
<td></td>
<td>- Use an activating antidepressant or a stimulant drug, if needed</td>
</tr>
<tr>
<td>Depression</td>
<td>- Encourage social and physical activities</td>
</tr>
<tr>
<td></td>
<td>- Treat underlying medical conditions (eg, hypothyroidism)</td>
</tr>
<tr>
<td></td>
<td>- Reduce and/or discontinue medications that may worsen depression (eg, antipsychotics, tetrabenazine)</td>
</tr>
<tr>
<td></td>
<td>- Use selective serotonin reuptake inhibitors (SSRIs), selective noradrenergic reuptake inhibitors (SNRIs), mirtazapine, and buspirone (consider that buspirone's dopamine reuptake inhibition may potentially worsen movement disorder and choreiform movements)</td>
</tr>
<tr>
<td>Irritable/aggressive symptoms</td>
<td>- Identify and treat comorbid conditions, including pain, medical, neurological, drug-related, substance-related, or psychiatric disorders</td>
</tr>
<tr>
<td></td>
<td>- Modify environmental factors, including an overstimulating environment</td>
</tr>
<tr>
<td></td>
<td>- Use behavioral strategies to prevent or reduce agitation or aggressive behaviors</td>
</tr>
<tr>
<td></td>
<td>- For acute agitation that responds poorly to behavioral strategies, consider a benzodiazepine or an antipsychotic</td>
</tr>
<tr>
<td></td>
<td>- For chronic agitation, use an antipsychotic or a mood-stabilizing anticonvulsant drug</td>
</tr>
<tr>
<td>Obsessive compulsive behaviors (OCBs)</td>
<td>- Modify environmental factors, including an overstimulating environment</td>
</tr>
<tr>
<td></td>
<td>- Use selective SSRIs, SNRIs, or clomipramine (anticholinergic adverse effect may further impair cognition), SNRIs</td>
</tr>
<tr>
<td></td>
<td>- Use antipsychotics in combination with SSRIs, clomipramine, or SNRIs to treat refractory OCBs</td>
</tr>
<tr>
<td>Psychotic symptoms</td>
<td>- Identify and treat comorbid conditions, including pain, medical, neurological, drug-related, substance-related, or psychiatric disorders</td>
</tr>
<tr>
<td></td>
<td>- Modify environmental factors, including an overstimulating environment</td>
</tr>
<tr>
<td></td>
<td>- Use behavioral strategies to prevent or reduce agitation or aggressive behaviors</td>
</tr>
<tr>
<td></td>
<td>- Use antipsychotics (preferably atypicals) to treat symptoms. Do not exceed dosing limits for drugs. Combining antipsychotic drugs is not recommended due to the significant risk for adverse effects</td>
</tr>
<tr>
<td></td>
<td>- Treatment with clozapine is recommended only for psychotic symptoms that are refractory to other antipsychotics</td>
</tr>
<tr>
<td>Anxiety symptoms</td>
<td>- Encourage social and physical activities</td>
</tr>
<tr>
<td></td>
<td>- Modify environmental factors, including an overstimulating environment</td>
</tr>
<tr>
<td></td>
<td>- Treat underlying medical conditions (eg, hyperthyroidism)</td>
</tr>
<tr>
<td></td>
<td>- Reduce or discontinue medications that may worsen anxiety (eg, buspirone)</td>
</tr>
<tr>
<td></td>
<td>- For acute anxiety, use benzodiazepines at the lowest effective dose for the shortest possible duration</td>
</tr>
<tr>
<td></td>
<td>- Use SSRIs, SNRIs, or mirtazapine for long-term treatment</td>
</tr>
<tr>
<td>Sleep disorders</td>
<td>- Identify and treat comorbid conditions, including pain, medical, neurological, drug-related, substance-related, or psychiatric disorders</td>
</tr>
<tr>
<td></td>
<td>- Modify environmental factors (eg, overstimulating environment)</td>
</tr>
<tr>
<td></td>
<td>- Use behavioral strategies to improve sleep (ie, sleep hygiene)</td>
</tr>
<tr>
<td></td>
<td>- If behavioral strategies do not help, consider melatonin, mirtazapine, quetiapine, olanzapine, or clomipramine</td>
</tr>
<tr>
<td></td>
<td>- Benzodiazepines are discouraged among ambulatory individuals except in refractory cases</td>
</tr>
<tr>
<td>Cognitive dysfunction</td>
<td>- Identify and treat comorbid conditions, including pain, medical, neurological, drug-related, substance-related, or psychiatric disorders</td>
</tr>
<tr>
<td></td>
<td>- Modify environmental factors, including an understimulating or overstimulating environment</td>
</tr>
<tr>
<td></td>
<td>- Use behavioral strategies, including the use of memory aids, to help prevent or reduce cognitive decline</td>
</tr>
<tr>
<td></td>
<td>- Use acetylcholinesterase inhibitors if the patient and their family agree, although results of controlled trials did not show benefit with these medications</td>
</tr>
</tbody>
</table>

*Symptoms include comorbidity and environmental factors.*

Neuropsychiatric symptom that is linearly related to progressive neurodegeneration. Additionally, the presence of all neuropsychiatric symptoms during the previous month was associated with a positive psychiatric history, and a past episode of depression was particularly associated with neuropysychiatric symptoms, except for psychosis.

**DEPRESSION.** Depressed mood, loss of interest, guilt, and suicidality were more indicative of depression than somatic symptoms (eg, poor appetite, sleep disturbances, and psychomotor slowing). In patients with HD, depression is more common among women.

Independent correlates of depression include a positive psychiatric history for depression, OCBs, a previous suicide attempt, and the use of benzodiazepines or antidepressants.

Suicidal ideation is also common in individuals with HD (Figure).

According to a recent review, lifetime rates of suicide attempts range from 6.4% to 16%, and the percentage of deaths from suicide range from 2.2% to 10%. The risk factors include the presence of psychiatric comorbidities, especially depression, followed by anxiety, aggression, and previous suicide attempt. Other related risk factors include irritability, apathy, OCBs, psychosis, history of suicidal ideation, alcohol abuse, and the use of antidepressants. No consistent evidence showed that the risk for suicide was associated with sex, ethnicity, having children, history of incarceration, severity of motor dysfunction, disease stage, and specific neuronal loss or pathophysiologic circuit.

Examining the neuropsychiatric symptoms in a European HD cohort (REGISTRY) study, 24.7% of individuals with HD reported mild irritability/aggression, and 13.9% reported moderate to severe irritability/aggression. The prevalence of moderate to severe irritability and aggression increased as disease stage progressed, from 10.4% in the milder stages to 19.6% in the later stages. Independent correlates included male sex, younger age, history of depression, psychosis, and a previous suicide attempt.

**OBSESSIVE-COMPULSIVE DISORDER.** One review found the prevalence of OCBs ranged from 5% to 52%, whereas perseverative behaviors (PBs) occurred in approximately 75% of the individuals. Individuals with premanifest HD reported more OCBs when compared with gene-negative controls. However, individuals with...
manifest HD reported a higher rate of OCBs when compared with those with premotor HD. Both OCBs and PBs are associated with duration and severity of HD, but they tend to decrease in the most advanced stage of the disease. A formal diagnosis of obsessive-compulsive disorder is also more prevalent than in the general population, and it is often classified as “obsessive-compulsive and related disorders due to another medical condition” using the DSM-5 criteria. OCBs tend to cause significant distress and impairment in functioning. PBs often occur without the individual’s full awareness or insight into their occurrence.

**PSYCHOSIS.** A recent study of 7966 participants with manifest HD found that 12.95% had a history of psychosis. Only 2.83% of participants with premotor HD had a history of psychosis. The mean age of psychosis onset was 48.34 years, and these individuals had mild-to-moderate psychosis. A family history of psychosis in a first-degree relative was documented in 27.5% of participants with psychosis. Factors associated with psychosis in manifest HD included lower education level, unemployment, single marital status, depression, decreased verbal fluency score, and decreased total functional capacity. Psychosis was also associated with younger age of HD diagnosis and younger age of motor symptom onset, and it was correlated with a general decrease in cognitive capacity.

**ANXIETY DISORDERS.** Available evidence indicates that between 13% and 71% of individuals may present with symptoms of anxiety. Anxiety can occur at any stage of the disorder, including the prodromal stage, but it does not appear to be a measure of disease progression. Anxiety may occur as a result of environmental factors as well as cognitive and physical impairments. It can also be confused with akathisia, which occurs as a result of medications (e.g., antipsychotics or tetrabenazine) used to treat HD symptoms.

**SLEEP DISORDERS.** Approximately 90% of individuals report sleep problems, including insomnia, difficulties in falling asleep, frequent nocturnal awakenings, and excessive daytime sleepiness. Available evidence indicates that some sleep disorders are found in the early phase of the disease, even during the illness’ premotor stage. These disorders may be associated with comorbid psychiatric disorders, especially mood and anxiety disorders. Involuntary movements and increased motor activity may also contribute to sleep difficulties. Many drugs that are used to improve the core symptoms of HD may also contribute to sleep disturbances, including amantadine, clonazepam, diazepam, L-DOPA olanzapine, quetiapine, risperidone, sodium valproate, tetrabenazine, and valproic acid.

**COGNITION.** Due to the degenerative nature of HD, individuals develop gradually progressive cognitive decline. Individuals develop the prototypical frontal-subcortical type of dementia, with frontal-executive disturbances, attentional deficits, and reductions in processing speed. These symptoms are the result of striatal and thalamic degeneration as well as degeneration in the caudate nucleus and putamen. As the illness progresses, abnormalities in visuomotor integration, visual perception, mental rotation, language production, and organization occur. However, the rate of progression of cognitive decline varies significantly among individuals, suggesting that other mechanisms (including environmental and genetic variables) may contribute to the neuropathological and clinical progression of cognitive decline.

**TREATMENT**

Available evidence indicates a comprehensive and multidisciplinary approach is required. Given the complexity of the illness’ clinical presentation, it should be treated by a group of providers including physicians, nurses, occupational and speech therapists, physical therapists, and social workers. Both nonpharmacological and pharmacological management strategies have benefited individuals with HD-associated neuropsychiatric symptoms. The use of nonpharmacological treatment strategies often complements pharmacological treatments. A thorough multidisciplinary team assessment can assist in identifying the environmental and medical triggers and causes of neuropsychiatric symptoms, which then can be used in developing individualized treatment plans. Cognitive dysfunction can be reduced by structured daily schedules, providing cues, and having regular routines. In addition, respite care may significantly relieve caregiver burden.

There are no controlled trials for the pharmacotherapy of neuropsychiatric manifestations of HD, but evidence has been gathered from published case reports, case series, and an expert-based consensus guideline (Table 2).

**Neuropsychiatric manifestations can occur decades before the motor symptoms become apparent and are associated with pathological changes that occur within the striatum and cortical regions of the brain.**

**Concluding Thoughts**

HD is a progressive and often fatal neurodegenerative disorder that is associated with severe motor and neuropsychiatric manifestations. The neuropsychiatric manifestations of HD can occur decades before the motor symptoms of HD become apparent, and they are associated with pathological changes that occur within the striatum and cortical regions of the brain, including the frontal lobes. Only apathy appears to be linearly related to the progressive neurodegeneration associated with HD. These manifestations are associated with significant disabilities and cause distress to both the individual with HD and their caregivers.

Currently, there are no disease-modifying strategies for the treatment of individuals with HD. Available treatment strategies focus on comprehensive multidisciplinary assessments and appropriate management of symptoms. There are no controlled studies for the treatment of neuropsychiatric manifestations of HD, but available evidence indicates efficacy for both nonpharmacological and pharmacological treatment modalities. The goal of treatment is to improve the quality of life for both the individual with HD and their caregivers.

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**REFERENCES**

Although vitamin deficiencies and their associated adverse effects are usually considered a public health problem in the developing world, they remain an important clinical consideration for select populations across the globe. In fact, there is concern that we may be confronted with increased negative consequences of poor nutrition due to decreased testing and screening and less education in our medical institutions about the importance of good nutrition to optimal health.

**Vital Amines**

Casimir Funk, PhD, discovered that key nutrients, which he termed *vital amines*, are essential to maintaining good health and that deficiencies in these key nutrients led to pathognomonic disease states. This realization was a result of observing birds that were fed a diet of polished rice and developed a diffuse polyneuritis (beriberi). The same birds were then fed a diet of brown rice, and their “nervous symptoms rapidly disappeared.” This experiment helped establish the importance of vital amines, later shortened to “vitamin.”

Vitamins can be broadly delineated into water-soluble and fat-soluble categories. Water-soluble vitamins are typically absorbed very quickly via the gastrointestinal tract and widely distributed in various tissues throughout the body. However, because these vitamins are water soluble, they are not efficiently stored in tissues. Therefore, this class of vitamins requires regular consumption (either through diet or supplementation) to avoid deficiency. Conversely, fat-soluble vitamins are more easily stored, typically in adipose tissue; therefore, they require less frequent intake. Examples of water-soluble and fat-soluble vitamins can be found in Table 1.

**What Is Vitamin B$_9$?**

Vitamin B$_9$, also known as folate or folic acid, is crucial for DNA synthesis and repair, as well as the metabolism of amino acids involved in methylation reactions. In women who are pregnant, the metabolism of amino acids involved in methylation reactions is crucial for DNA synthesis and repair, as well as the development of neural tube defects in the fetus. In adults, folate deficiency can result in multiple neuropsychiatric symptoms. These symptoms may include cognitive impairment, insomnia, psychosis, depression, peripheral sensory deficits, and weakness. These manifestations are very similar to those of vitamin B$_12$ deficiency. In patients with depression, folate deficiency can contribute to severity and can impede depression treatment.

**What Causes Folate Deficiency?**

Folate, which is absorbed in the small intestine, is obtained via diet or supplementation. Select food sources of folate or folic acid can be found in Table 1. Most serum folate is found in its active form, methyltetrahydrofolate (methyl THF). Methyl THF undergoes a B$_12$-dependent enzymatic reaction, donating its methyl group to form tetrahydrofolate, which, in turn, is later involved in DNA formation. Any disruption in this process can lead to a deficiency in folate and its associated manifestations.

Folate deficiency can manifest from several different causes. High anabolic states, such as pregnancy, can result in increased utilization and depletion of folate stores. Similarly, chronic alcohol abuse causes poor absorption, impaired metabolism, and increased destruction of folate. Even moderate amounts of alcohol (for instance, 8 oz of red wine or 2.7 oz of vodka per day for a 2-week period) have been shown to reduce folate levels in otherwise healthy men. Certain medications have been shown to contribute to folate deficiency. A summary of common medications as well as their mechanism of folate deficiency can be found in Table 3.

**Who Is at Risk?**

Patients who appear to be at highest risk for deficiency include individuals with alcohol dependence; individuals who take the noted medications (Table 3); patients who require increased intake of folate (eg, pregnancy, hemodialysis, chronic anemias); and those patients with poor absorption because of intestinal dysfunction from surgery or inflammatory bowel syndromes. Women of child-bearing age are also considered to be at risk. According to the National Health and Nutrition Examination Survey, nearly 20% of women aged 14 to 30 years have inadequate serum levels of folate. The survey also found that almost 25% of non-Hispanic Black women have insufficient intake of folate compared with 13% of non-Hispanic White women.

### Table 1. Water-soluble vs Fat-soluble Vitamins

<table>
<thead>
<tr>
<th>WATER SOLUBLE</th>
<th>VS</th>
<th>FAT SOLUBLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>B$_1$ (thiamine)</td>
<td>B$_2$ (riboflavin)</td>
<td>B$_3$ (niacin)</td>
</tr>
</tbody>
</table>

---

**Figure. Homocysteine and MMA Pathways**

CoA, coenzyme A; MMA, methylmalonic acid; THF, tetrahydrofolate.
Table 2. Select Food Sources of Folate and Folic Acid

<table>
<thead>
<tr>
<th>Food</th>
<th>Percent daily value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinach, boiled, ½ cup</td>
<td>33%</td>
</tr>
<tr>
<td>Asparagus, boiled, 4 spears</td>
<td>22%</td>
</tr>
<tr>
<td>Brussels sprouts, frozen, boiled, ¼ cup</td>
<td>21%</td>
</tr>
<tr>
<td>Lettuce, romaine, shredded, 1 cup</td>
<td>16%</td>
</tr>
<tr>
<td>Avocado, raw, sliced, ½ cup</td>
<td>15%</td>
</tr>
<tr>
<td>Spinach, raw, 1 cup</td>
<td>15%</td>
</tr>
<tr>
<td>Broccoli, chopped, frozen, cooked, ¼ cup</td>
<td>13%</td>
</tr>
<tr>
<td>Peanuts, dry roasted, 1 ounce</td>
<td>10%</td>
</tr>
<tr>
<td>Orange, fresh, 1 small</td>
<td>7%</td>
</tr>
<tr>
<td>Papaya, raw, cubed, ½ cup</td>
<td>7%</td>
</tr>
<tr>
<td>Banana, 1 medium</td>
<td>6%</td>
</tr>
<tr>
<td>Cantaloupe, raw, 1 wedge</td>
<td>4%</td>
</tr>
<tr>
<td>Beef liver, braised, 3 ounces</td>
<td>54%</td>
</tr>
<tr>
<td>Egg, whole, hard boiled, 1 large</td>
<td>6%</td>
</tr>
<tr>
<td>Fish, halibut, cooked, 3 ounces</td>
<td>3%</td>
</tr>
<tr>
<td>Chicken breast, roasted, ½ breast</td>
<td>1%</td>
</tr>
<tr>
<td>Black-eyed peas (cowpeas), boiled, ½ cup</td>
<td>26%</td>
</tr>
<tr>
<td>Green peas, frozen, boiled, ½ cup</td>
<td>12%</td>
</tr>
<tr>
<td>Kidney beans, canned, ¼ cup</td>
<td>12%</td>
</tr>
<tr>
<td>Vegetarian baked beans, canned, ½ cup</td>
<td>4%</td>
</tr>
<tr>
<td>Milk, 1% fat, 1 cup</td>
<td>3%</td>
</tr>
<tr>
<td>Yogurt, whole milk, plain, ½ cup</td>
<td>2%</td>
</tr>
<tr>
<td>Breakfast cereals, fortified</td>
<td>25%</td>
</tr>
<tr>
<td>Rice, white, medium grain, cooked, ½ cup</td>
<td>23%</td>
</tr>
<tr>
<td>Spaghetti, cooked, enriched, ½ cup</td>
<td>21%</td>
</tr>
<tr>
<td>Bread, white, 1 slice</td>
<td>11%</td>
</tr>
</tbody>
</table>

Table 3. Select Common Medications Associated With Folate Deficiency

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Inhibit folate metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mechanism</td>
</tr>
<tr>
<td></td>
<td>Antineoplastic agents</td>
</tr>
</tbody>
</table>
| Methotrexate              | Measured serum and MMA levels are elevated because B12 is involved in only homocysteine pathway (Figure). Clinically elevated homocysteine can result in increased risk of thrombosis and its complications, such as myocardial infarction. Oral replacement of folate is the recommended treatment. If the patient is unable to take oral medications, intravenous repletion is acceptable. The typical dose is dependent on the deficiency severity but ranges from 1 mg to 5 mg daily. Folate-deficient megaloblastic anemia due to dietary insufficiency or medications should be treated with up to 5 mg of folic acid daily for 4 months. Patients with malabsorptive states should be treated with up to 15 mg daily for 4 months.

Dr Elbasheer is a research coordinator in the Department of Behavioral Health Research at John Peter Smith Health Network in Fort Worth, Texas. The authors report no conflicts of interest.

REFERENCES

What About Prevention?
Screening and testing should occur in individuals who are at high risk, have evidence of a macrocytosis or hyper-segmented neutrophils, and have unexplained neuropsychiatric conditions (eg, weakness, ataxia, paresthesia, dementia, delirium, and depression).
Folic acid supplementation is recommended for all individuals who are at high risk. Evidence suggests that pregnant women should take at least 600 μg of folic acid daily to prevent neural tube defects. Folic acid is also typically given to patients on methotrexate to reduce adverse effects, although the dose given varies among rheumatologists. Patients with chronic hemolytic states and renal dialysis are recommended to take 5 mg daily to weekly, depending on requirement.

What About Folate Deficiency?
In 2018, a systematic review of survey data examined global folate status in women of childbearing age. Despite methodological limitations such as nonuniform measurement techniques and/or cutoff values, Rogers et al determined that the prevalence of folate deficiency was more than 20% in lower income countries and less than 5% in higher income countries. In January 1998, the United States implemented a mandate to fortify grain products with folate in an effort to reduce the incidence of folic acid deficiencies. Since then, folate deficiency has become very rare in the United States, with a prevalence of less than 1%.
CLINICAL

Breaking the Spell: Fighting Myths About COVID-19 Vaccination

Lubna Khawaja, MD; Syed Iqbal, MD; Asim Shah, MD; and Nidal Moukaddam, MD, PhD

To help in the prevention of the coronavirus disease 2019 (COVID-19), the Food and Drug Administration (FDA) issued an emergency use authorization (EUA) for the Pfizer-BioNTech vaccine on December 11, 2020. One week later, the FDA authorized the Moderna COVID-19 vaccine. The availability of vaccines against COVID-19 has provided a sense of optimism, as many have endured prolonged isolation and quarantine, the mental health effects of the pandemic, and the morbidity and mortality of the disease. However, for vaccines to achieve the desired effect there must be a minimum number of individuals who accept it. Vaccine hesitancy is not a new issue; it has been widely studied. In fact, the World Health Organization identified it as 1 of the top 10 global health threats in 2019.1

A large survey by the Pew Research Center found the intent to get the COVID-19 vaccine dropped from 72% in May 2020 to 51% by September 2020.2 Of those respondents, 77% reported a concern that vaccine would be prematurely approved without long-term safety data. Among the individuals who did not want the vaccine, 76% expressed concern about its potential adverse effects, whereas 72% wanted to know more about its efficacy before administration. Of the individuals who intended to get the vaccination, 19% expressed a great deal of confidence about safety and efficacy, 45% reported a fair amount of confidence, and 35% reported not much or no confidence at all (Figure 1).3 The intent to get vaccinated increased in December 2020, as 60% of Americans said that they would “definitely” and “probably” get COVID-19 vaccination once it is possible.4

More recently, the Kaiser Family Foundation (KFF) surveyed 1676 adults in the United States from November 30 to December 8, 2020. They found that 71% of respondents reported they would “definitely” or “probably” get the COVID-19 vaccine, whereas 27% expressed concern and were hesitant to receive it.5 The sample was randomized to represent the population, including Hispanic and non-Hispanic Black adults. Vaccine hesitancy was high in individuals identifying as Republicans (42%), rural residents (35%), and Black adults (35%) (Figure 2).6 For comparison, during the 2009 influenza A H1N1 pandemic, the early estimates of vaccine acceptability were between 50% and 64%.7 To address lagging hesitancy and resistance, vaccine myths and disinformation need to be addressed, and clear and consistent messages should be delivered to the community about the importance of receiving the vaccine. Psychiatrists can and should take time to address these issues with their patients.

Types of Vaccines

Messenger RNA (mRNA) vaccines. In the 2 COVID-19 vaccines currently available, the mRNA carries instructions to make the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) attach, or spike, protein to the host cells. After the vaccine is injected, the mRNA is taken up by the macrophages near the injection site and instructs these cells to make the spike protein. This spike protein then appears on the surface of the macrophages inducing an immune response.8

Viral vector vaccines. These types of vaccines take another virus and replace its genetic material with the sequence coding for the SARS-CoV-2 spike protein. The virus acts as a delivery system, or vector, for this genetic sequence.9

Replication-defective adenovirus vector vaccines. The AstraZeneca/Oxford University vaccine uses a simian adenovirus vector, and the Johnson & Johnson vaccine uses a human adenovirus vector to carry the DNA coding for the spike protein to the host cells and deliver it to the nucleus.10 The cell’s machinery produces the spike protein, which then induces the immunologic response.11 The virus contained in this vaccine does not replicate inside cells, as the genes responsible for replication have been deactivated. These vaccines are not authorized in the US.

Protein subunit vaccines. These include SARS-CoV-2 spike protein but no genetic material. Novavax’s investigational vaccine, NVX-CoV2373, is made from recombinant nanoparticle-studded with coronavirus spike proteins.12 It is awaiting results from phase 3 trials from multiple sites.

COVID-19 Vaccine Safety

The mRNA vaccines are classified as...
resect anxiety, paranoia, and even delusions in the context of vaccine hesitancy. Widespread conspiracy thinking can make it more difficult to achieve proper control of the pandemic and promote adherence to healthy behaviors. Vigilant fact-checking and challenging irrational thinking are essential. Stressful circumstances could trigger or exacerbate mental illness, and the debunking of vaccine-related myths should include an assessment of whether the beliefs represent mental symptoms that need treatment.

Anxiety about vaccine safety and adverse effects correlates with increasing scores on the Vaccine Conspiracy Belief Scale, obtaining information from social media, and lower educational status. Conspiratorial beliefs are inversely correlated with adhering to safety restrictions and behaviors, and related to pseudoscientific practices and vaccine hesitancy. Studies also found that individuals with strong COVID-19 conspiracy beliefs tended to have lower education. The right framing can present the vaccine as a gain instead of a risk. The concept of using mRNA as a novel therapeutic tool dates to the early 1990s. The mRNA is not designed to integrate with host DNA, nor can it typically do so given its rapid degradation. In the COVID-19 vaccine, once the immune response is initiated against the spike protein, mRNA is degraded by the cells. The vaccine will alter my DNA/make me infertile. The concept of using mRNA as a novel therapeutic tool dates to the early 1990s. The mRNA is not designed to integrate with host DNA, nor can it typically do so given its rapid degradation. In the COVID-19 vaccine, once the immune response is initiated against the spike protein, mRNA is degraded by the cells. The concept of using mRNA as a novel therapeutic tool dates to the early 1990s. The mRNA is not designed to integrate with host DNA, nor can it typically do so given its rapid degradation. In the COVID-19 vaccine, once the immune response is initiated against the spike protein, mRNA is degraded by the cells.

Mental Illness Exacerbation in Context of Vaccine Hesitancy

Mental health professionals can expect anxiety, paranoia, and even delusions in the context of vaccine hesitancy. Widespread conspiracy thinking can make it more difficult to achieve proper control of the pandemic and promote adherence to healthy behaviors. Vigilant fact-checking and challenging irrational thinking are essential. Stressful circumstances could trigger or exacerbate mental illness, and the debunking of vaccine-related myths should include an assessment of whether the beliefs represent mental symptoms that need treatment.

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Table 2. Myths About COVID-19 Vaccination

<table>
<thead>
<tr>
<th>Myth</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The vaccine will alter my DNA/make me infertile.</td>
<td>76%</td>
</tr>
<tr>
<td>2. I already had COVID-19, so I do not need the vaccine.</td>
<td>72%</td>
</tr>
<tr>
<td>3. Not everyone with COVID-19 dies, so I will be fine without the vaccine.</td>
<td>19%</td>
</tr>
<tr>
<td>4. By taking the vaccine I will get the COVID-19 infection or will test positive for COVID-19.</td>
<td>45%</td>
</tr>
<tr>
<td>5. The vaccine may make me psychotic or have a microchip.</td>
<td>35%</td>
</tr>
<tr>
<td>6. Vaccines cannot be trusted, as they were rushed in the process of their development.</td>
<td>Not much confidence, or none at all</td>
</tr>
</tbody>
</table>

Figure 1. Concerns and Confidence About the Vaccines

<table>
<thead>
<tr>
<th>Concerns about adverse effects</th>
<th>76%</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONFIDENCE IN THE VACCINES’ SAFETY AND EFFICACY</td>
<td>72%</td>
</tr>
<tr>
<td>19% A great deal of confidence</td>
<td>45% A fair amount of confidence</td>
</tr>
<tr>
<td>35% Not much confidence, or none at all</td>
<td></td>
</tr>
</tbody>
</table>

Confronting and Overcoming Vaccine Myths and Misconceptions

A survey conducted by the Yale New Haven Health System showed that 1 out of 6 health care workers expressed reluctance to getting the vaccine in the first wave, with the most common reason being medium- and long-term safety issues. Health care staff also expressed concerns about lack of existing research and data transparency, uncertainty about the inclusion of minority groups in the trials, a rushed process, RNA technology, underlying or preexisting conditions not studied, political influence, and length of expected immunity from the vaccine. The KFF’s vaccine monitoring system found similar hesitancy trends in the general population. A probing yet nonconfrontational approach combined with directing individuals toward objective resources may work best in addressing some of the common misconceptions. Motivational interviewing techniques can also tackle vaccine hesitancy.

“The vaccine will alter my DNA/make me infertile.” The concept of using mRNA as a novel therapeutic tool dates to the early 1990s. The mRNA is not designed to integrate with host DNA, nor can it typically do so given its rapid degradation. In the COVID-19 vaccine, once the immune response is initiated against the spike protein, mRNA is degraded by the cells.

“Vaccines cannot be trusted, as they were rushed in the process of their development.” During the clinical trials, the companies used the vaccine in a large sample of volunteers to establish its safety and efficacy. It took a few months for the clinical trials to collect substantial data, which was further scrutinized by the experts in the FDA, and the 2 vaccines received EUA. In addition, many vaccine safety monitoring systems are in place: the V-safe, National Healthcare Safety Network, and others are tasked with identifying adverse events not encountered in clinical trials. The only missing piece, in fact, is long-term effectiveness data, as most adverse effects with vaccines

Figure 2. Groups Hesitant to Receive the Vaccine

<table>
<thead>
<tr>
<th>Group</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Republicans</td>
<td>42%</td>
</tr>
<tr>
<td>Rural residents</td>
<td>35%</td>
</tr>
<tr>
<td>Black adults</td>
<td>35%</td>
</tr>
</tbody>
</table>
Swift Action: A Look at President Biden’s Health Care Executive Orders

» Keith A. Reynolds

The newly minted White House administration wasted no time in enacting its health care agenda, as President Joseph R. Biden Jr. signed a flood of executive orders during his first 48 hours in office. Among the top priorities are the nation’s coronavirus disease 2019 (COVID-19) response and mental health issues.

Here is a look at some of Biden’s actions since taking office:

IMPROVING AND EXPANDING ACCESS TO COVID-19 CARE AND TREATMENTS. This order directs officials to support studies and clinical trials for new COVID-19 interventions, create recommendations for expanding health care facility capacity, and improve access to quality and affordable treatments.

ENACTING DATA-DRIVEN RESPONSE TO COVID-19. The heads of all executive departments and agencies are ordered to help in the gathering and dissemination of COVID-19 data to assist in the pandemic response. Because this order also seeks to improve public health data collection and analytics going forward, it also orders them to help enhance data collection and collaboration capabilities in future public health threats.

SHORING UP THE PUBLIC HEALTH SUPPLY CHAIN. Biden invoked the Defense Production Act to inventory all COVID-19 response supplies, take steps to address pricing of pandemic response supplies, and facilitate the access to the strategic national stockpile by independent people.

PROTECTING WORKER HEALTH AND SAFETY. Using the Occupational Safety and Health Act, the secretary of labor will issue revised guidance to employers on workplace safety during the COVID-19 pandemic.

PROHIBITING DISCRIMINATION BASED ON GENDER IDENTITY AND SEXUAL ORIENTATION. Advocates and mental health care professionals believe this will help improve the overall well-being for LGBTQ populations.

OPENING A SPECIAL ENROLLMENT PERIOD FOR A NEW SUBSIDIZED HEALTH INSURANCE PLAN. This allows people who are uninsured to log on to the federal website and choose a health plan to obtain insurance, which especially has importance with the pandemic.

These are just a sample of the actions taken, and it is believed that Biden will continue to tackle mental health issues, including the opioid crisis.

Read more at: https://bit.ly/3ccy7Bv
**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™ and a MAOI intended to treat psychiatric disorders at the same time.

**DOSE 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 (e.g., 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: 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) include 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., Cranbury, NJ 08512

PM-US-DRI-0099
Exercise and Cognition in Schizophrenia: Is There a Link?

Brian Miller, MD, PhD, MPH

Recently, there is limited evidence for significant pro-cognitive effects of antipsychotics and other pharmacologic approaches. Therefore, treatment of cognitive impairment in schizophrenia represents a tremendous area of unmet need.

There has been significant research on the effects of exercise on brain structure and functional performance. A meta-analysis found that aerobic exercise exerted a positive effect on global cognition and some, but not all, cognitive domains in patients with schizophrenia. Unfortunately, findings are limited by small samples, as well as variable types and intensity of exercise and study designs.1

Aerobic Exercise

A supervised aerobic walking program was receptive to the recommendations because of her clinical improvement. Mrs Morris declined to lower the dose of her antipsychotic or change medications because of her clinical improvement. She worried about risk of an- other illness relapse. However, she was receptive to the recommendation for increased physical activity for transportation are associated with re- lase. She reported feeling better functionally divided over 3 to 5 sessions and each with a 5-minute warm-up, fol- lowed by a 5-minute cool-down. Transportation was provided to the exercise sessions as needed. Participants wore a Fitbit to monitor heart rate and exercise intensity and were supervised by research staff who provided guidance based on heart rate. The patients could rest if needed. Participants were stratified into high- and low-intensity groups based on the average in-session heart rate re- serve. Cognition was evaluated with the Brief Assessment of Cognition in Schizophrenia (BACS).

Data were analyzed using intention-to-treat and per-protocol analyses. Multivariate general linear model repeated measures were used to investi- gate the effects of time, group, and the time x group interaction on cognition, controlling for illness du- ration. The authors randomized 67 patients to treatment as usual (TAU, n = 31) or aerobic walking (n = 33) who completed the baseline assessment. Thirty-three patients in the TAU and 31 in the aerobic walking group com- pleted the 12-week trial (Table). At baseline, participants in the aerobic walking group scored approximately 0.5 standard deviations lower on global cognition than the TAU group. The mean duration of aerobic walking was 129 minutes/week. Eleven patients achieved high-intensity walking and 22 maintained low-intensity. In the entire intent-to-treat sample, the authors found a trend for a group effect for greater improve- ment in verbal fluency in the aerobic walking group. They also found a significant group effect on attention and processing speed in high- versus low-intensity aerobic walking.

Exploring the Findings

This was the first trial of the effects of aerobic walking and exercise intensity on cognitive function in schizophrenia, according to the study authors. Most (> 90%) patients completed the trial with a mean of 3 days of exercise per week. The findings suggest that this treatment is feasible and acceptable to patients, and that supervision and transportation are associated with re- lationship. Study limitations included the modest sample size (especially in the high-intensity group) and a relatively short study duration, as well as the inability for blinding to the intervention.

The Bottom Line

A supervised aerobic walking program involving moderate-intensity exercise is feasible and acceptable in patients with schizophrenia. Higher intensity aerobic exercise may have modest pro- cognitive effects in these patients. Consider- ing the other health benefits of aerobic walking, these programs can be useful for patients with schizophrenia.

REFERENCES


CASE VIGNETTE

“Mrs Morris” is a 48-year-old Black woman with a history of chronic schizophrenia. During hospitalization for an episode of illness exacerbation, her antipsychotic medication was modified. Over the next 4 months, she gained approximately 50 lb. Mrs Morris declined to lower the dose of her antipsychotic or change medications because of her clinical improve- ment. She worried about risk of an- other illness relapse. However, she was receptive to the recommenda- tion for increased physical activity for transportation are associated with re- lase. She reported feeling better functionally divided over 3 to 5 sessions and each with a 5-minute warm-up, fol- lowed by a 5-minute cool-down. Transportation was provided to the exercise sessions as needed. Participants wore a Fitbit to monitor heart rate and exercise intensity and were supervised by research staff who provided guidance based on heart rate. The patients could rest if needed. Participants were stratified into high- and low-intensity groups based on the average in-session heart rate re- serve. Cognition was evaluated with the Brief Assessment of Cognition in Schizophrenia (BACS).

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BIPOLAR UPDATE

Addressing Smoking: Is Varenicline the Answer?

David N. Osser, MD

Many patients with bipolar disorder (BD) have comorbid substance use disorders, including nicotine use. Some reports suggest 70% of patients with BD smoke. Importantly, data show that continuing to smoke reduces the chances of successfully addressing other substance use. The mechanisms of nicotine and other substances are similar, so it is necessary to stop all substances that are maintaining the pathological processes. Patients, and some clinicians, erroneously believe it is OK to wait to address cigarette and other nicotine use.

The most effective smoking cessation medication is varenicline. The EAGLES study, a randomized, double-blind, placebo-controlled trial (N=8144) compared varenicline, bupropion, and nicotine replacement therapy (NRT). The results confirmed many smaller studies that varenicline treatment had the best outcome (defined as abstinence at weeks 9-12). The investigators also studied the effects among various diagnoses by dividing patients into 2 equal cohorts—one with and the other without psychiatric disorders (70% unipolar and bipolar mood disorders, 20% anxiety disorders, and 10% psychotic disorders). The study found varenicline performed the best of the 4 treatments in both groups. In the nonpsychiatric cohort, abstinence rates were 38% for varenicline vs 26% on other active treatments and 14% on placebo. In the psychiatric cohort, abstinence occurred in 29% on varenicline, 19% to 20% on the other medications, and 11% on placebo.

The safety results may surprise some clinicians and patients. No differences were reported in moderate to severe neuropsychiatric adverse effects (eg, depression, suicidality, aggression) between varenicline and placebo in either cohort. In fact, as a result of the EAGLES findings, the US Food and Drug Administration removed the longstanding black box warning regarding such adverse effects. Interestingly, these neuropsychiatric adverse events can occur, but they are not more common if the patient is on varenicline. The effects are proposed to be due to nicotine withdrawal. These safety results are consistent with many other studies, and the call to “stop ringing the alarm bell” was in the literature even before EAGLES. Previous studies included patients with stabilized BD, and findings showed excellent efficacy and safety regarding precipitation of mood swings. There seem to be no significant drug interactions with any bipolar medications.

If smoking cessation fails on varenicline, controlled studies have shown augmentations with NRT or bupropion can add efficacy. Bupropion, however, is probably not a good choice for a patient with BD. The preferred augmentation would be NRT with patch and oral agents followed by slow taper; this strategy may blunt the nicotine withdrawal and increase success rates.

One minor adverse effect of varenicline is insomnia. Nightmares and disturbed awakenings associated with posttraumatic stress disorder (PTSD) may increase with varenicline. Before initiating varenicline, sleep disturbance associated with PTSD should be managed with prazosin. Five out of 8 placebo-controlled studies have found efficacy for prazosin. (Prazosin for PTSD in BD will be discussed in a future article: dosing and procedures with prazosin are best exemplified by Raskind et al.) Prazosin may need to be increased if the nightmares reappear or increase after starting varenicline.

The hydrocarbons in cigarette smoke increase the activity of cytochrome P450 1A2, which metabolizes olanzapine and clozapine. Smoking cessation will, therefore, result in gradual deinduction of this enzyme, and plasma levels of these antipsychotics will increase over a week or 2.

Dr Osser is associate professor of psychiatry at Harvard Medical School and colead psychiatrist at the US Department of Veterans Affairs, National Telemental Health Center, Bipolar Disorders Telehealth Program, Brockton, Massachusetts.

REFERENCES

Mood Disorders

Psychiatric Residency Interview

—Boston, 1976

The elevator squeaks up to seven, worn carpet, a muffled, Come in! when I knock and enter a room dimmed to twilight, Freud’s bust, the graybeard interviewer’s face blurred in shadow, his hand waving me toward a chair angled to obscure him from view, and he gives a strange command: Tell me a little bit about yourself. Only a little bit? At a job interview? But his head is nodding Yes, and I talk—med school for psychiatry, patients I loved, books that kidnapped my attention, growing up with a sick father, and the helpless feeling I’d become a doctor and still couldn’t save him, the professor laying low in shadow, breathing Hmmm, Uh-huh, in rhythm with my words until that moment an hour deep when he suddenly stands and thanks me for coming in, for sharing so much, my life pasted on his wall to analyze, the flash of insight: training had begun.

Dr Berlin has been writing a poem about his experience of being a doctor every month for the past 23 years in Psychiatric Times® in a column called “Poetry of the Times.” He is instructor in psychiatry, University of Massachusetts Medical School, Worcester, Massachusetts.
National Awards Honor Psychiatric Times™ Editorial Board Members

» Laurie Martin

Leading psychiatric organizations have recognized the commitment and exemplary work of Psychiatric Times™ Editorial Board members.

Jack Weinberg Memorial Award in Geriatric Psychiatry

The American Psychiatric Association (APA) and the APA Foundation have selected Rajesh R. Tampi, MD, MS, DFAPA, as the recipient of the 2021 Jack Weinberg Memorial Award in Geriatric Psychiatry. The award, instituted in 1983, recognizes a psychiatrist who has devoted their career to geriatric psychiatry. The awardee also exemplifies leadership and goes above and beyond in the areas of clinical practice, educational training and mentorship, and important research.

Tampi’s passion—to promote the care of older adults with mental health disorders and to train the next generation of leaders in psychiatry and geriatric psychiatry—certainly falls within these parameters. His clinical interests include not only late-life psychiatric disorders but also legal matters and ethics, neurodegenerative disorders, and integrated geriatric-psychiatric care. He has been a proponent of undergraduate and postgraduate education in both psychiatry and geriatric psychiatry.

“I am honored and humbled to receive the award,” Tampi told Psychiatric Times™. “It was the support of Cleveland Clinic, the Yale School of Medicine, the American Association of Geriatric Psychiatry, and the APA that has allowed me the opportunity to pursue my passion for clinical excellence, teaching, mentorship, research, writing, and advocacy,” he added.

When asked what drew him to geriatric psychiatry as a specialty, Tampi replied, “It provides the science and art of healing.”

Tampi is chairman of the Department of Psychiatry & Behavioral Sciences, Cleveland Clinic Akron General in Akron, Ohio. He also is professor of medicine, Cleveland Clinic Learner College of Medicine of Case Western Reserve University, as well as professor of psychiatry at North East Ohio Medical University. He is adjunct professor of psychiatry at Yale School of Medicine, New Haven, Connecticut.

In addition to his appointment as Geriatric Psychiatric Section Editor for Psychiatric Times™, Tampi is editor-in-chief of the World Journal of Psychiatry and associate editor of Drugs in Context (Psychiatry). He is also copresident of the American Association for Geriatric Psychiatry. A prolific writer, Tampi’s published works include nearly 200 publications and 46 book chapters; he also is editor of 9 books in psychiatry. His most recent book is Absolute Geriatric Psychiatry Review: Essential Questions and Answers (Springer International Publishing; 2021).

Tampi lives in Ohio, with his wife Deena, a frequent collaborator with him on articles and book projects, and their children Alexa, Vaishnav, Julia, Olivia, Peki, Smoki, and Oreo Cookie.

All award recipients will be recognized in the online 2021 American Psychiatric Association Annual Meeting Convocation.

Seymour Pollack Award

The American Academy of Psychiatry and the Law (AAPL) presented James L. Knoll IV, MD, with the Seymour Pollack Award, for notable achievements in the education and teaching of forensic psychiatry. The award was presented at the 51st AAPL Annual Meeting.

Knoll, director of forensic psychiatry and professor of psychiatry at State University of New York (SUNY) Upstate Medical University in Syracuse, said he was honored and humbled to receive the award. He added that it was the support of AAPL, SUNY Upstate, and New York State’s Office of Mental Health that has allowed him the opportunity to pursue his passion for teaching, writing, and forensic investigation. He added that the award further inspires him to explore the interface between psychiatry and the law, as well as to train the next generation of forensic psychiatrists.

Editor in chief emeritus of Psychiatric Times™ from 2010 to 2014, Knoll is a nationally recognized expert in forensic psychiatry who has made significant contributions to the research on mass murder and violence. He is chair of the Threat Assessment Subcommittee of the Syracuse School Safety Task Force and has spoken nationally and consulted with law enforcement, including the Department of Justice, the National Institute of Justice, and the Federal Bureau of Investigation (FBI).

Knoll is one of only a handful of psychiatrists in the country to be accepted as an associate fellow of the International Criminal Investigative Analysis Fellowship; the fellowship meets regularly at the FBI National Academy in Quantico, Virginia. Before moving to New York, he was the director of Psychiatric Treatment Services for the New Hampshire state prison system, where he was responsible for the oversight of New Hampshire’s insanity acquittie patient population. Knoll has served as an expert witness in cases of national prominence, such as the “Cleveland Strangler” serial murder case of Anthony Sowell, and the “137 shots” Cleveland Police shooting case. He has served as a stalking risk assessment consultant for law enforcement and for victims of stalking for more than 20 years.

A prodigious writer, Knoll’s works include:

- Articles for Psychiatric Times™, including the series “Tales From the New Asylum.”
- Articles for the Correctional Mental Health Report, (for which he served as coeditor and contributing editor).
- Textbooks about forensic psychiatry, including Principles & Practice of Forensic Psychiatry, The Oxford Textbook of Correctional Psychiatry, the Textbook of Forensic Psychiatry, and Clinical Assessment of Malingering and Deception.
- A vast compendium of articles on the Jonestown mass murder-suicide.

REFERENCES


Do you know someone in psychiatry who has been honored with an award? Please share the good news with us by emailing PTEditor@mmhgroup.com.
Important Safety Information

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

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

Warnings & Precautions: Antipsychotic drugs have been reported to cause:

- **Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis**, including stroke and transient ischemic attack. See Boxed Warning above.
- **Neuroleptic Malignant Syndrome**, which is a potentially fatal reaction. Signs and symptoms include: hyperpyrexia, muscle rigidity, delirium, autonomic instability, elevated creatinine phosphokinase, myoglobinuria (and/or rhabdomyolysis), and acute renal failure. Manage with immediate discontinuation of CAPLYTA and provide intensive symptomatic treatment and monitoring.
- **Tardive Dyskinesia**, a syndrome of potentially irreversible, dyskinetic, and involuntary movements which may increase as the duration of treatment and total cumulative dose increases. The syndrome can develop after a relatively brief treatment period, even at low doses. It may also occur after discontinuation of treatment. Given these considerations, CAPLYTA should be prescribed in a manner most likely to reduce the risk of tardive dyskinesia. Discontinue CAPLYTA if clinically appropriate.
- **Metabolic Changes**, including hyperglycemia, diabetes mellitus, dyslipidemia, and weight gain. Hyperglycemia, in some cases extreme and associated with ketoacidosis, hyperosmolar coma or death, has been reported in patients treated with antipsychotics. Measure weight and assess fasting plasma glucose and lipids when initiating CAPLYTA and monitor periodically during long-term treatment.
- **Leukopenia, Neutropenia, and Agranulocytosis (Including Fatal Cases)**. Perform complete blood counts in patients with pre-existing low white blood cell count (WBC) or history of leukopenia or neutropenia. Discontinue CAPLYTA if clinically significant decline in WBC occurs in absence of other causative factors.
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Choose CAPLYTA to help control your patients’ symptoms—with a metabolic, weight, and EPS profile similar to placebo in 4- to 6-week trials¹

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

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

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

**Adverse Reactions:** The most common adverse reactions in clinical trials with CAPLYTA vs. placebo were somnolence/sedation (24% vs. 10%) and dry mouth (6% vs. 2%).

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


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Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of mortality. A meta-analysis of 17 placebo-controlled trials (includes pooled data from placebo-controlled trials and clinical trials of at least 6 months duration) of antipsychotic drugs showed a risk increase of approximately 2.5 (95% CI 1.3 to 4.7) for deaths associated with all causes in patients treated with antipsychotics. The risk was highest for older patients and patients with dementia.

In pooled data from placebo-controlled trials, the risk of mortality in patients with dementia treated with antipsychotics was higher than in those treated without antipsychotics. In addition, antipsychotics may cause somnolence and has the potential to impair judgment, thinking, and motor skills. In short-term (i.e., <4- to 6-week) placebo-controlled trials of elderly patients treated with antipsychotics, the risk of mortality in patients with dementia treated with antipsychotics was 2.5 times higher than in those treated without antipsychotics.

Whether antipsychotic drug products differ in their ability to cause death in the elderly is unknown. All antipsychotics should be used with caution in patients with dementia.


table 2 in the full prescribing information displays drugs having clinically important interactions with CAPLYTA. Moderate or Strong CYP3A Inducers: Concomitant use of CAPLYTA with CYP3A inducers may result in decreased CAPLYTA plasma concentrations. CYP3A inducers include carbamazepine, rifampin, phenobarbital, phenytoin, St. John’s wort, and cyclosporine.

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Exploring Psychiatry and the Human Condition

Aftab Aftab, MD

Joanna Moncrieff, MD, is professor of critical and social psychiatry at University College London and works as a consultant in community psychiatry in London. She has researched and written about theories of drug action, drug efficacy, the subjective experience of taking psychiatric drugs; decision-making; the history of drug treatment; and the history, politics, and philosophy of psychiatry more generally. She is currently leading a United Kingdom (UK) government-funded study of antipsychotic reduction and discontinuation, called the RADAR study (Research into Antipsychotic Discontinuation and Reduction). She is one of the founders and the co-chairperson of the Critical Psychiatry Network. She has authored numerous papers and several books including The Myth of the Chemical Cure (Palgrave Macmillan, 2008); The Bitterest Pills: The Troubling Story of Antipsychotic Drugs (Palgrave Macmillan, 2013); and A Straight-Talking Introduction to Psychiatric Drugs (PCCS Publishers, 2013).

Moncrieff’s views on psychopharmacological mechanisms of action, although controversial, have been influential within the critical psychiatry community. We have discussed some implications of the drug-centered model in an earlier interview with Sandra Steingard, MD. Moncrieff’s ongoing randomized controlled trial investigating the long-term impact of gradual antipsychotic dose reduction and discontinuation in schizophrenia on outcomes such as psychotic relapse and social functioning (versus maintenance treatment) could alter how the field approaches management of chronic psychotic disorders.

This interview, however, largely focuses on conceptual concerns, exploring her views on the nature of psychiatric suffering. My first conscious exposure to Moncrieff was at the 2017 annual meeting of the Association for the Advancement of Philosophy and Psychiatry, where Moncrieff gave the keynote lecture titled “Many Ways of Being Human,” in which she challenged the medical view of mental disorders and argued that medical and psychiatric conditions have a different relationship to agency, responsibility, and selfhood.

Moncrieff’s ideas carry on the legacy of Thomas Szasz, MD, and given my own disagreements with how Szasz conceptualizes the notion of disease, this interview also represents an attempt on my part to understand how deep our philosophical disagreements go.

The article in Philosophy, Psychiatry, & Psychology referred to by Moncrieff was in press at the time this interview was conducted but has since been published online. I would also like to add that there is a large body of literature critically engaging with the ideas of Thomas Szasz, such as the 2019 book Thomas Szasz: An Appraisal of his Legacy (International Perspectives in Philosophy and Psychiatry; 2019), which I would encourage readers to explore.

AFTAB: Can you briefly tell us about the Critical Psychiatry Network? Its mission and how it has impacted British psychiatry over the years?

MONCRIEFF: When I was a trainee in psychiatry, I felt the way psychiatry was portrayed in the mainstream—in textbooks and medical journals—did not match my ideas about the nature of mental health problems or my experience of individuals who were deemed to have such problems. I was aware that other trainees felt like this too, so I started a club while I was at the Institute of Psychiatry in 1997. Initially we had discussions about interesting books and articles, and then we organized meetings, in conjunction with the Maudsley Hospital service-users group, with outside speakers, including the likes of Szasz, Nikolas Rose, PhD, and Andrew Scull, PhD. Around this time, we were contacted by some psychiatrists from another part of the UK, who were concerned about the upcoming review of the Mental Health Act. We got together to submit evidence to this review, and that was the start of the Critical Psychiatry Network.

Since that time, it has functioned as a forum for mutual support, and as a mechanism for contributing a critical view of psychiatric practice to various parliamentary and governmental reviews, the media, and other organizations. Have we had any impact? I think the fact that members of the psychiatric profession are challenging mainstream views, particularly the dominance of the biological paradigm in psychiatry, is important, and helps to support broader movements that are trying to imagine and establish alternative approaches.

AFTAB: Models of drug action have been an important focus of your work—in particular, the distinction between the disease-centered model and drug-centered model. In the disease-centered model, drugs help correct an abnormal brain state and the therapeutic effects of drugs are derived from their effects on an underlying disease process. In the drug-centered model, drugs are psychopharmacological agents that create an abnormal brain state, and therapeutic effects are derived from the impact of drug-induced states on behavioral and emotional problems. Can you elaborate for us how your framework incorporates such hypotheticals?

MONCRIEFF: I think I make it clear in my writings that the disease-centered model I have outlined is not restricted to what we think of as diseases, especially as the use of this term in psychiatry is not clear-cut. The disease-centered model consists of the idea that drugs work by targeting underlying biological mechanisms that produce what we call the symptoms of mental disorders. Hence, your thought experiment is an example of the disease-centered model as I have noted.

My response to your example is this: First of all, we have no idea what biological mechanism mediates anhedonia or almost any other subjective experience. The idea that we can pin down the biological mechanisms of complex human thoughts, feelings, and behaviors is part of the problem with our thinking. We cannot do this now, and we have no indication that we will be able to do so in the future—a view put forward in critical neuroscience too, by the way.1,2

Second, if you give a drug that affects mechanisms P, Q, R, S and some others, and through its action produces an altered mental state in anyone who takes it regardless of diagnosis, allowing for individual variation, you will get some impact on emotions, including feelings of anhedonia. This may involve mechanisms related to anhedonia,
- There is no need to postulate a hypothetical disease-centered action alongside it.

**AFTAB:** What is your view of the philosophy of psychiatry literature that has emerged, in general, and in particular thinking of the way we express our worldly situation, not from the nature of the biochemical or physiological reactions.

**MONCRIEFF:** I have followed the work of Fulford and, to a lesser extent, the others you mention in detail over the past few decades and I am about to have a paper published in the journal *Philosophy, Psychiatry, & Psychology* that responds to their work. I cannot do justice here. Certainly, some mental processes are not straightforwardly voluntary. Our moods and emotions, for example, are not brought on at our demand. Yet, although feelings are usually unbidden, we can nevertheless usually exercise some control over how we behave in response to them, and, often, with time and experience, over the feelings themselves. In the normal course of things, we see our moods and emotions as being part of ourselves or our character. As I put it in my recent paper “the way we express our emotions is part of what is characteristic about us as individuals.”

**AFTAB:** What about psychological experiences that are involuntary, unwanted, and distressing, such as auditory hallucinations and obsessions? At least in some instances, they are perceived to be intrusive and threatening to their sense of selves and lead to help-seeking behaviors. Do you think of those experiences as part of the self or reflective of the individual’s values, desires, and intentions?

**MONCRIEFF:** This is a good question, and it highlights the complexity of our human nature, which I cannot do justice here. Certainly, some mental processes are not straightforwardly voluntary. Our moods and emotions, for example, are not brought on at our demand. Yet, although feelings are usually unbidden, we can nevertheless usually exercise some control over how we behave in response to them, and, often, with time and experience, over the feelings themselves. In the normal course of things, we see our moods and emotions as being part of ourselves or our character. As I put it in my recent paper “the way we express our emotions is part of what is characteristic about us as individuals.”

**AFTAB:** We know that psychosis can occur in conditions such as Parkinson disease and Alzheimer disease, and there are phenomenological similarities between psychosis in these instances and the psychosis experienced in schizophrenia. I assume you consider the former pair to be diseases but the latter the former? If we restrict ourselves to examining

- Biological processes are not meaningful, but biology is the context in which human agency takes place, and it sets the limits of possibility.
the psychotic experiences only, without considering the concomitant presence of motor or cognitive symptoms, is there anything in the nature of these psychotic experiences that tells you whether they should be considered a disease or not?

MONCRIEFF: Physical states can occasionally mimic psychological ones. Thyroid hormone deficiency is famously said to cause depression. Often there are some phenomenological differences, but probably not always. Amphetamine abuse can cause psychosis. Again, there are some phenomenological differences if you were to look at a group level, but you cannot necessarily distinguish amphetamine-induced psychosis from an idiopathic psychotic episode on the basis of symptoms alone. However, this does not mean that the majority of instances of psychosis and depression are of the same nature.

Interpretation of feelings and events may be quite different from the subject’s and this is not an arena where we can ever know the truth as we know it in a physical science.

I take issue with your statement that “there is no philosophical reason why meaning and biological abnormalities should be considered mutually exclusive,” and I argue this point in my recent paper. We are biological beings, and our behavior and activity is reflected in our biology, so of course “meaning and biological abnormalities” coexist. Yet, when we think of behavior, biological causation trumps meaning and agency. If an action—a twitch or a seizure, for example—is caused by a biological process, this removes it from the realm of agency. It does not make sense to think of an action as both caused by a biological reflex and initiated by the self in an intentional fashion. They are mutually incompatible situations.

MONCRIEFF: I would put it another way. Despite decades of extremely well-funded research, we have yet to identify any specific biological factor associated with any type of mental disorder, including schizophrenia. There is a genetic component to many things, and it is likely this includes some aspects of character or temperament that are associated with developing schizophrenia. As far as other research goes, despite what you and others say, findings are not well replicated, and the research has failed to control for crucial confounding factors such as drug treatment, social class, stress, and IQ.

There are myriad reasons why individuals who show unusual behavior that is classified as schizophrenia are likely to have higher rates of obstetric complications, inflammatory markers, dopamine abnormalities, drug use, etc., when compared with stable, employed, middle class individuals that become the normal controls in biological studies. The most consistent and well-replicated finding in individuals with schizophrenia is the evidence of smaller brain size and larger brain ventricles, yet after years of talk about “schizophrenic brains,” it transpires that this is, at least in large part, caused by antipsychotic drug treatment.

AFTAB: Thank you!

Conversations in Critical Psychiatry’s aim is to engage prominent experts within and outside the profession who have made meaningful criticisms of psychiatry and have offered constructive alternative perspectives to the current status quo. The opinions expressed in the interviews are those of the participants and do not necessarily reflect the opinions of Psychiatric Times.

Dr Aftab is a psychiatrist in Cleveland, Ohio, and clinical assistant professor of psychiatry at Case Western Reserve University. He is a member of the executive council of Association for the Advancement of Philosophy and Psychiatry and has been actively involved in initiatives to educate psychiatrists and trainees on the intersection of philosophy and psychiatry. He is also a member of the Psychiatric Times Advisory Board. He can be reached at awaisaftab@gmail.com or on Twitter @awaisaftab.

Dr Aftab and Moncrieff have no relevant financial disclosures or conflicts of interest. Dr Moncrieff discloses that she is the cochairperson of the Critical Psychiatry Network, a board member of the Council for Evidence-Based Psychiatry, chief investigator on the RADAR study of antipsychotic reduction funded by the UK government’s National Institute of Health Research (NIHR) and co-investigator on the REDUCE study of antidepressant discontinuation also funded by the NIHR.

REFERENCES
Psilocybin Revisited: The Science Behind the Drug and Its Surprising Therapeutic Potential

Michael W. Jann, PharmD, FCP

Psilocybin and psilocin are the main psychodelic agents of the psychoactive mushroom genus *Psilocybe*. Historical and cultural use of these psychoactive mushrooms dates back 3000 years in Mexico and the southwestern regional areas of the present-day United States. Scientifically, psilocybin was isolated and identified in 1958, synthesized in 1959, and used in various experimental research studies in the early 1960s. During that time, psilocybin and other psychodelic agents such as lysergic acid diethylamide (LSD) generated considerable controversy. Outside of recreational use, could they be used safely as therapeutic interventions?

The pharmaceutical company Sandoz ceased LSD and psilocybin manufacturing in 1965, and in 1970, the Controlled Substances Act placed psilocybin, LSD, and other psychodelic drugs under the Schedule I designation. This action resulted in a cessation of research associated with these agents. The revival of research into psilocybin and LSD began 25 years later under strict restrictions, when preliminary findings displayed promising results for a variety of psychiatric disorders. In the past several years, there have been more research studies on psychodelics than at any previous time.

The FDA approved the psychodelic agent, esketamine nasal spray for treatment-resistant depression (TRD) in 2019; this opened the door to the novel therapeutic approaches of psychodelic agents. In 2018, the FDA designated psilocybin for TRD and 3,4-methylenedioxyamphetamine (MDMA)-assisted psychotherapy for post-traumatic stress disorder (PTSD) as breakthrough therapies. Based on these recent studies and approvals, psilocybin may have a growing role in the treatment of TRD and other psychiatric disorders. Psilocybin reportedly has a low abuse potential and yields no physical dependence, based on the 8 factors of the Controlled Substances Act. It was recommended to be rescheduled as a Controlled Substance Schedule IV drug with a risk evaluation

**Significance for Psychiatrists**

- Psilocybin is considered a prodrug, which is an inactive agent, that is rapidly converted in the body to psilocin, the active ingredient that produces psychological and behavioral effects.
- Psilocin’s pharmacologic action occurs as that of a selective 5-HT2A receptor agonist, and it is primarily eliminated from the body by renal excretion with an elimination half-life of about 3 hours.
- Typically, psilocybin is administered as a single oral dose, with 2 dose administrations and a specific time interval of several weeks between the 2 doses.
- In small clinical pilot studies, psilocybin displayed benefits for treatment-resistant depression and a variety of other psychiatric conditions.
- Based upon these potential benefits, psilocybin is under clinical development for such psychiatric disorders.
- Psilocybin is administered under the psychodelic-assisted psychotherapy method.

**ACTIVITY GOAL**
The goal of this activity is to inform readers about the latest research and clinical trials on psilocybin and outline its possible clinical uses.

**LEARNING OBJECTIVES:**
1. Describe the active ingredient of psilocybin.
2. Discuss the pharmacology and pharmacokinetic profile of psilocybin.
3. Recognize the potential clinical applications of psilocybin for treatment-resistant depression and other psychiatric conditions.
4. Identify the psychodelic-assisted psychotherapy method for psilocybin treatment.

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

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

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mitigation strategy (REMS) if approved by the regulatory agencies.6,6

Pharmacology

The structures of psilocybin (O-phosphoryl-4-hydroxy-N,N-dimethyltryptamine) and its active metabolite psilocin (4-hydroxy-N,N-dimethyltryptamine) are shown in the Figure, and they both belong to the group of tryptamine/indolamine hallucinogens that are related to serotonin.4 Psilocybin can be considered a prodrug, as it is rapidly converted to psilocin in the gastrointestinal (GI) tract by alkaline phosphatase and nonspecific esterases, where 1.0 mol of psilocybin is equal to 1.4 mol of psilocin.4 Psilocin is the active molecule that produces the pharmacologic effects of a selective agonist of serotonin (5-HT) receptors, which include 5-HT1A, 5-HT2A, 5-HT2C, and 5-HT3 receptors.7,10 Compared to other similar 4-OH substituted tryptamines, psilocin has the most potent binding affinity (Ki) for 5-HT1A receptors (6.0 nM), 5-HT2C receptors (10 nM), and to a lesser extent, 5-HT3 receptors (410 nM).1,7

Preclinical studies have shown that 5-HT1A receptor activation in the cortical and subcortical structures is the unifying mechanism by which psychedelics exert their hallucinogenic and other assorted psychological actions.5 Depending upon the dose used, the specific psychedelic agent, and possibly, the 5-HT1A receptor density in the different neuronal areas, psilocybin and other psychoactive agents can exert different modulatory actions across the various cortical regions. The administration of ketanserin (a 5-HT1A receptor antagonist) in human clinical studies attenuated the psychological effects of psilocybin, psilocin, and LSD.1,5 The role of 5-HT1A receptors in human psilocybin studies remain to be elucidated.

Besides 5-HT receptors, psychedelic agents may possess other pharmacologic actions that contribute to their behavioral and psychological effects. LSD was reported to interact with considerable affinity at the dopamine receptor with stereospecificity, as d-LSD was 1000 times more potent than l-LSD.1 A positron emission tomography (PET) study examined the use of psilocybin in healthy volunteers (N=7) and its effects on in vivo D2 receptor binding using 11C-raclopride in the striatum. Dosed at 0.25 mg/kg orally, psilocybin produced changes in mood, thinking disturbances, illusions, and visual hallucinations.4 Psilocybin also significantly decreased 11C-raclopride binding potential bilaterally in the caudate nucleus (19%) and putamen (20%), which was consistent with a reciprocal increase in endogenous dopamine. These findings indicate that 5-HT1A receptor activation can be a factor for modulating striatal dopamine release in acute psychosis. Psilocybin may be a useful pharmacologic agent for examining the complex interactions between serotonin-dopamine systems and various psychiatric conditions, such as schizophrenia.

The activation of 5-HT2A postsynaptic receptors by psilocybin is also believed to increase glutamate release by the subsequent activation of postsynaptic α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors.7 The prefrontal cortex (PFC) and other cortical areas that highly express 5-HT1A receptors receive excitatory glutamatergic input from thalamic projections, but also send output to both the cortical and thalamic regions. The activation of presynaptic 5-HT2A receptors in the thalamocortical afferents contributes to the psychedelic-induced modulation of glutamatergic transmission to the PFC. Thus, these dual actions from the presynaptic and postsynaptic 5-HT2A receptors form a cyclic feedback process for 5-HT1A receptor activation of glutamate effects in the central nervous system, leading to a complex cortical-thalamic neurocircuitry.7

Pharmacokinetics

Psilocybin is rapidly converted to the active molecule, psilocin. Specific bioanalytical assay methods have been developed to quantify psilocin, to determine its pharmacokinetic (PK) profile. An early study with psilocybin was conducted in healthy volunteers (N = 7), in which each participant received an intravenous (IV) dose of 1 mg and an oral dose of 0.224 mg/kg (range 10 to 20 mg).1 The estimated mean oral bioavailability of psilocin was 52.7% ± 20%. The following mean PK parameters reported from the oral route were the time to maximum effect/concentration (Tmax) of 105 ± 37 min; peak plasma concentration (Cmax) of 8.2 ± 2.8 ng/mL; and elimination half-life (T1/2β) of 163.3 ± 63.5 min. An almost immediate phosphorylation of psilocybin takes place, and results from the IV administration noted a mean psilocin T1/2β of 1.9 ± 1.0 min; Cmax of 12.9 ± 5.6 ng/mL; and Tmax of 74.1 ± 19.6 min. The psychological effects reported began at 20 to 90 min, and within 2 min from the oral and intravenous routes, respectively.

In a population PK study, healthy volunteers (N = 12) were given escalating single oral doses of psilocybin at 0.3, 0.45, and 0.6 mg/kg, with a minimum of a 4-week interval between dosage administrations.12 The final model developed from the PK analysis was a single compartment model with linear absorption and clearance. The median area under the concentration-time curve (AUC) for psilocin was linear at 140 μg·hr/L, 213 μg·hr/L, and 267 μg·hr/L, corresponding to the doses of 0.3 mg/kg, 0.45 mg/kg, and 0.6 mg/kg, respectively. Once psilocin is formed, it is mainly metabolized to psilocin-G (90%), and a small portion is converted to psilocin (10%). This can partially explain the interpatient variability observed with psilocybin administration. The study reported only 1.7% of the psilocybin dose found as psilocin in the urine, with a calculated psilocin renal clearance of 1 mL/min/kg, which corresponds to 58% of the creatinine clearance.13 These findings suggest that psilocybin dosage reductions are not necessary in patients with mild to moderate renal impairment.
The metabolic profile of psilocybin is presented in the Figure. It shows that after conversion to psilocin, several metabolic routes are possible. As noted, psilocin-G is the major pathway (bold arrow line) with 2 minor pathways.1,5 Psilocin-G formation occurs via phase 2 metabolism with hepatic uridine 5’-diphospho (UDP)-glucuronosyltransferase (UGT) 1A9 and the small intestine UGT1A10.

In the second minor pathway, psilocin can be metabolized to 4-hydroxy-indole-3-acetdehyde by 2 enzymes: aldehyde dehydrogenase (ALDH) and monoamine oxidase (MAO). It should be noted that alcohol and MAO inhibitors such as phentazolene may suggest interesting questions regarding potential drug-drug interactions that can lead to pharmacokinetic and/or pharmacodynamic effects. The metabolite, 4-hydroxy-indole-3-acetic acid and 4-hydroxytryptophole.16

The third minor metabolic pathway for psilocin takes place via the cytochrome oxidase enzymes (it is unknown whether this is related to the cytochrome P450 oxidase enzymes) and non-enzymatic Fe3+ to form psilocin iminoquinone.6

Clinical Drug Development

Earlier PK studies established the initial parameters for psilocybin dosing and provided information on the onset of its psychological effects for drug and product development. The next steps are to correlate the psilocybin (psilocin) clinical PK effects with its pharmacodynamics. A PET study conducted on healthy volunteers (N = 8) who were given oral psilocybin (doses ranging from 3 mg to 30 mg) evaluated plasma psilocin concentrations, while assessing 5-HT2A receptor occupancy.13 Participants self-assessed their intensity ratings for clinical effects using a Likert scale from 1 to 10. Participants self-assessed their intensity ratings for visual hallucinations.1 It would be interesting to determine how the actions of pimavanserin, an antagonist of serotonin 5-HT4 and 5-HT2A receptors. Pimavanserin is FDA-approved for Parkinson disease psychosis, for which hallucinations (visual and auditory predominately) and illusions occur.18

Table 1. Summary of Psilocybin Clinical Studies

<table>
<thead>
<tr>
<th>Condition</th>
<th>N</th>
<th>Dose</th>
<th>Design</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-resistant depression</td>
<td>12</td>
<td>10 mg, 25 mg</td>
<td>Open-label</td>
<td>Significant improvement; clinical rating scores; single doses given 2 weeks apart</td>
</tr>
<tr>
<td>Cancer, anxiety/depression*</td>
<td>92</td>
<td>0.2 mg/kg, 0.3 mg/kg, 22 or 30 mg/70 kg</td>
<td>RDBC RDBC RDBC</td>
<td>6-month follow-up noted sustained benefit with significant in clinical rating scores</td>
</tr>
<tr>
<td>Tobacco use disorder</td>
<td>15</td>
<td>20 or 30 mg/70 kg</td>
<td>Open-label</td>
<td>At 6 months, noted 80% of participants had lab-verified abstinence; 1 year later 67%</td>
</tr>
<tr>
<td>Alcohol use disorder</td>
<td>10</td>
<td>0.3 or 0.4 mg/kg</td>
<td>Open-label</td>
<td>Significant noted in drinking behavior noted for up to 9 months</td>
</tr>
<tr>
<td>Obsessive-compulsive disorder</td>
<td>9</td>
<td>4 different doses 0.025-0.3 mg/kg</td>
<td>Open-label</td>
<td>Improvement noted but not dose-dependent; each patient received all 4 doses</td>
</tr>
</tbody>
</table>

*Adapted from references 2, 17, 24, and 25. 3 different clinical studies combined.

For the psilocybin TRD study,23 treatment-resistant was defined as Hamilton Depression Rating Scale (HAM-D) scores > 17 and a lack of improvement with 2 different classes of antidepressant medications for at least 6 weeks within the current episode. A single dose of psilocybin 10 mg, followed by 25 mg 7 days later was administered. Clinical assessments were obtained at baseline, at 7 days with administration of the second dose, and at 3 months after the second dose. The primary efficacy outcome was determined by the Quick Inventory of Depressive Symptomatology (QIDS), and the secondary outcomes were determined by the HAM-D and Beck Depression Inventory (BDI).

A phase 2b clinical trial is underway in the United States and Europe, with additional clinical trials planned.

Psilocybin significantly reduced the mean (± SD) QIDS scores at 1 week (−11.8 ± 4.9, P = 0.002) and at 3 months (−9.2 ± 6.0, P = 0.003). The study also resulted in significantly reduced HAM-D and scores.23 At the 1-week mark, remission (defined as reduction in BDI score of 5) was achieved in 8 patients (67%). At the 3-month follow-up, remission (defined as a 50% reduction in BDI score) was achieved in 7 patients (58%); 5 patients (42%) reached complete remission. Psilocybin was well tolerated and the psychological effects were transient and consistent with those observed in previous studies. Although significant changes in vital signs were not found,16 prior studies reported the following adverse effects with psilocybin 8 to 12 mg: mydriasis, change in heart rate, hypotension or hypertension, nausea, reflex tendencies, and tremors.14 Furthermore, if participants experienced significant hallucinations, illusions, or other psychotic symptoms, treatment with second-generation antipsychotic agents, such as risperidone or olanzapine, was suggested.16 Haloperidol was reported to alleviate only the euphoric, depersonalization, or derealization effects and not the visual hallucinations.1 It would be interesting to determine the actions of pimavanserin, an antagonist of serotonin 5-HT4 and 5-HT2A receptors. Pimavanserin is FDA-approved for Parkinson disease psychosis, for which hallucinations (visual and auditory predominately) and illusions occur.18

Esketamine is a noncompetitive N-methyl D-aspartate (NMDA) receptor antagonist that is FDA-approved for treatment-resistant depression (TRD). Esketamine underwent a phase 2 proof-of-concept study and then proceeded to the phase 3 clinical trials.2,17,19,20 TRD was defined as a failure to adequately respond to 2 different antidepressants.

Esketamine is administered twice weekly at doses of 56 mg or 84 mg. Each clinical trial had treatment groups administered placebo nasal spray plus an oral antidepressant or esketamine nasal spray plus an oral antidepressant. Therefore, each patient continued to receive treatment with an antidepressant as the standard of care. From a safety perspective, esketamine was well tolerated. However, the incidence of dissociation reactions was reported to be about 23%.21 Esketamine is available via the REMS program; patients must be monitored for 2 hours after nasal spray administration for safety.22

These findings regarding esketamine led to the development of psilocybin for TRD. The drug and product development process for psilocybin will likely take a similar approach. An initial open-label psilocybin study in patients with TRD (N = 12) was conducted using 2 psilocybin doses of 10 mg and 25 mg.22 The psilocybin doses selected for TRD are comparable to those for other psychiatric disorders under evaluation (Table 1).17,19,25

For a phase 2b clinical trial it is underway in the United States and Europe, with additional clinical trials planned.

The third minor metabolic pathway for psilocybin was also reported to be about 23%.21 Esketamine is available via the REMS program; patients must be monitored for 2 hours after nasal spray administration for safety.22

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Psilocybin may be useful for examining interactions between serotonin-dopamine systems and various psychiatric conditions, such as schizophrenia.

### Table 2. Summary of the Psychedelic-Assisted Psychotherapy Session*

<table>
<thead>
<tr>
<th>Component</th>
<th>Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preparatory</td>
<td>Therapist or co-therapist team engages the patient and prepares them for experience with an emphasis on potential emotional and psychological growth. Patient education of expectations during the psychedelic session is reviewed.</td>
</tr>
<tr>
<td>Medication</td>
<td>This process can have 1-3 sessions with moderate to high psilocybin doses. Therapists accompany the patient for safety and record the patient’s comments and reactions. Drug is given in a comfortable room and patient is monitored for the next 6-8 hours. Therapist's goals are to maintain safety, trust, and openness.</td>
</tr>
<tr>
<td>Integration</td>
<td>Therapists work with patient to interpret the content of the psychedelic experience with meaningful long-term changes via identifying insights and interpreting thoughts or ideas that occurred during the session.</td>
</tr>
</tbody>
</table>

*Adapted from Reference 22.

**Psilocybin**

Psilocybin has been assessed in small studies for the treatment of patients with treatment-resistant depression (N = 25). No serious adverse events were observed, and improvements in depression (≥ 50% decrease from baseline) were seen up to 9 months. The study was expanded to enroll up to 180 participants with completion scheduled for 2020 or 2021.25 Additional psilocybin clinical trials have been conducted for cocaine and opioid disorders, anorexia nervosa, and depression in early Alzheimer disease.25 Another suggested therapeutic use of psilocybin may be for cluster headaches.27

**Psychedelic-Assisted Psychotherapy**

Unlike previous clinical trials in psychopharmacology, the use of psychedelic agents, such as psilocybin, LSD, and MDMA, will employ a therapeutic technique called “Psychedelic-Assisted Psychotherapy,” which is summarized in Table 2.22-26 This technique consists of 3 sections: preparatory, medication administration (1 to 3 sessions), and integration. In the preparatory section, the therapist or cotherapist team works with the patient to obtain a personal history, help the patient understand their symptoms, and prepare for the potential emotional or psychological impact of the agent. During the medication session, a female-male cotherapy team is present to maintain integrity and safety, with the patient reclined in a chair or bed.
For the next 6 to 8 hours, the therapists listen to the patient, while maintaining safety and facilitating trust and openness. Afterward, the therapists in the integration session work with the patient to interpret the psychedelic experience that arose, with the goal of meaningful long-term changes. If the patient becomes highly agitated during the 6- to 8-hour period after psilocybin administration, while responding to the hallucinations or other psychological effects, a physician or nurse should immediately assess the need for either a single low-dose second-generation antipsychotic (eg, risperidone) or pimavanserin as a rescue medication.

Microdosing is another technique for psilocybin use. With this technique, about one-tenth of the full dose is used. Psilocybin dosing ranges are as follows: microdose, <1 mg; very low dose, 3 mg; low dose, 8 mg; medium dose, 15 mg; and high dose, 22 mg or greater. Although microdosing has been studied in small open-label studies with doses administered about once every 3 to 5 days, it is unclear how this technique differs from the full dose administered for depression and other psychiatric disorders.29,30

Concluding Thoughts
Psilocybin has received considerable renewed interest over the past few years and has been investigated as a treatment for TRD and other psychiatric conditions. Exploring the use of psilocybin for treatment has been studied in small open-label studies and has been investigated for the rapid reduction of symptoms of depression and suicidality in patients at imminent risk for suicide: results of a double-blind, randomized, placebo-controlled study. Am J Psychiatry. 2018;175(7):820-830.

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“Ocean Medical Center’s psychiatry program will be a community-based program,” said Ramon Solkkah, M.D., program director for psychiatry as well as founding Chair of Psychiatry & Behavioral Health at the Hackensack Meridian School of Medicine at Seton Hall University. “Our new psychiatry residency program will improve clinical care and ultimately encourage future health care leaders to build practices in the Jersey Shore area.”

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**FLORIDA UNIVERSITY OF MIAMI, DEPARTMENT OF PSYCHIATRY EXCEPTIONAL PSYCHIATRY OPPORTUNITY Addiction Psychiatrist**

The Department of Psychiatry and Behavioral Sciences at the University of Miami announce a search for an academic psychiatrist with interest and experience in Addiction Psychiatry. Applicants with clinical translational research background and track record of funding are encouraged.

**JOB DESCRIPTION**

We are seeking an Associate Professor or equivalent to take on a leadership role in the Department as Division Chief for Addiction Psychiatry and Director of the Addiction Fellowship.

**QUALIFICATIONS OF THE PSYCHIATRIST**

- Board certification in Psychiatry.
- Board eligibility/certification in Addiction Psychiatry
- Demonstrated record of experience and training in addiction psychiatry.

**COMPENSATION & BENEFITS**

This dynamic position commands an extremely competitive 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 401(k) plans.

The University of Miami (UM) Miller School of Medicine is an academic medical center with extensive clinical facilities including the UHealth system, Jackson Memorial Hospital, and the Miami VA Hospital. Department psychiatrists 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: Carmen Alsina at calsina@med.miami.edu
NEW HAMPSHIRE

Child/Adolescent Psychiatrist

Beautiful Seacoast area with four seasons, 55 minutes from Boston. Expanding private, non-profit community mental health center seeks a Child/Adolescent Psychiatrist to join a staff of ten psychiatrist sand 4 APRN’s, for outpatient care. Vibrant collegial atmosphere with competitive salary and benefits. Interested candidates apply at: https://smbc-nh.org/job-openings
EOE M/F

SOUTH CAROLINA

Child & Adolescent Psychiatrist

Greenville, SC

Prisma Health, the largest healthcare provider in South Carolina, currently seeks BC/BE Child & Adolescent Psychiatrists to join our growing psychiatry department. The department is expanding our clinical, education, and research missions and is seeking candidates in all specialties. Successful candidates will have the opportunity to work within our specialty outpatient clinics and/or programs, and work across disciplines with other departments. Ideal candidates will have an interest in teaching and be eligible for faculty appointment at University of South Carolina School of Medicine Greenville, located on Prisma Health’s Greenville Memorial Medical Campus.

Details Include:
• Candidate must be fellowship-trained and board certified (or eligible) in Psychiatry
• Experience in an outpatient mental health setting, including telepsychiatry services
• Monday - Friday Outpatient with 1:7 weekend inpatient coverage
• Academic faculty position working with fellows, residents and medical students
• Competitive compensation
• Rich benefits package including relocation, malpractice, health and dental insurance
• CME allowance

Prisma Health employs 16,000 people, including 1,200+ physicians on staff. Our system includes clinically excellent facilities with 1,627 beds across 8 campuses. Additionally, we host 19 separate research facilities.

Greenville, South Carolina is a beautiful place to live and work and the Prisma Health 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: Natasha Durham, Physician Recruiter, Natasha.Durham@PrismaHealth.org, ph: 864-797-6114

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

WYOMING

$17,000.00 - $20,833.34 Monthly

The Wyoming Department of Health offers an excellent benefits package, including medical/dental/vision insurance, paid sick leave and paid holidays, state retirement plan, deferred compensation program and longevity pay.

AGENCY REQUIREMENTS
• Doctor of Medicine (M.D. or D.O.)
• Board certified (or eligible) in Psychiatry
• Eligible for licensure to practice medicine in Wyoming.

Contact:
Tara Gerrard, Physician Recruiter
tara.gerrard@wy.gov
307-789-3464 ext 656

Click here to view the State of Wyoming Classification and Pay Structure.
URL: http://agency.governmentjobs.com/wyoming/default.cfm
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- Drizalma Sprinkle™ can be administered with or without food. Capsules can be opened, and the contents sprinkled over applesauce

Dosing and Administration

- Drizalma Sprinkle™ is available in 4 dosage strengths—20 mg, 30 mg, 40 mg, and 60 mg—for flexibility and easy titration
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IMPORTANT SAFETY INFORMATION (cont’d)

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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.

DOZING 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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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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