The law presumes that individuals are rational. The reasonable individual, a hypothetical figure whose actions judges and juries weigh against others, will lucidly consider risks versus benefits before acting. Yet, we know that neuropsychiatric impairment can impede the capacity for making these calculated judgments, and in some cases this impairment is associated with a lack of illness awareness (or “insight”) that affects adherence with treatment.

Accounting for Privacy With Neuropsychiatric Impairments

The law presumes that individuals are rational. The reasonable individual, a hypothetical figure whose actions judges and juries weigh against others, will lucidly consider risks versus benefits before acting. Yet, we know that neuropsychiatric impairment can impede the capacity for making these calculated judgments, and in some cases this impairment is associated with a lack of illness awareness (or “insight”) that affects adherence with treatment.

“I’m Homeless and I Have PTSD”

In this installment of Tales From the Clinic: The Art of Psychiatry, we examine the case of posttraumatic stress disorder (PTSD) in the setting of homelessness and substance use. Most homeless individuals report experiencing significant trauma at some point in their lives.

Continued on page 9

Continued on page 10


**INDICATION**

Auvelity is indicated for the treatment of major depressive disorder (MDD) in adults.

**IMPORTANT SAFETY INFORMATION**

**WARNING: SUICIDAL THOUGHTS AND BEHAVIORS**

- Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric and young adult patients in short-term studies.
- Closely monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors.
- Auvelity is not approved for use in pediatric patients.

**CONTRAINDICATIONS**

Seizure: Do not use Auvelity in patients with a seizure disorder.

Current or prior diagnosis of bulimia or anorexia nervosa: A higher incidence of seizure was observed in such patients treated with bupropion.

Undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs: Due to risk of seizure.

Monoamine Oxidase Inhibitors (MAOIs): Do not use Auvelity concomitantly with, or within 14 days of stopping, an MAOI due to the risk of serious and possibly fatal drug interactions, including hypertensive crisis and serotonin syndrome. Conversely, at least 14 days must be allowed after stopping Auvelity before starting an MAOI antidepressant. Do not use Auvelity with reversible MAOIs such as linezolid or intravenous methylene blue.

Hypersensitivity: Do not use in patients with known hypersensitivity to dextromethorphan, bupropion, or any component of Auvelity. Anaphylactic/anaphylactoid reactions and Stevens-Johnson syndrome have been reported with bupropion. Arthralgia, myalgia, fever with rash, and other serum sickness-like symptoms suggestive of delayed hypersensitivity have also been reported with bupropion.

**WARNINGS AND PRECAUTIONS**

**Suicidal Thoughts and Behaviors in Pediatrics and Young Adults:** Monitor all antidepressant-treated patients for any indication for clinical worsening and emergence of suicidal thoughts and behaviors, especially during the initial few months of drug therapy, and at times of dosage changes. Counsel family members or caregivers of patients to monitor for changes in behavior and to alert the healthcare provider. Consider changing the therapeutic regimen, including possibly discontinuing Auvelity, in patients whose depression is persistently worse, or who are experiencing emergent suicidal thoughts or behaviors.

Seizure: Bupropion, a component of Auvelity, can cause seizure and the risk is dose related. Because the risk of seizure with bupropion is dose-related, screen patients for use of other bupropion-containing products prior to initiating Auvelity. If concomitant use of Auvelity with other bupropion-containing products is clinically warranted, inform patients of the risk. Discontinue Auvelity and do not restart treatment if the patient experiences a seizure.

**Increased Blood Pressure and Hypertension:** Treatment with bupropion, a component of Auvelity, can cause elevated blood pressure and hypertension. The risk of hypertension is increased if Auvelity is used concomitantly with MAOIs or other drugs that increase dopaminergic or noradrenergic activity. Assess blood pressure before initiating treatment with Auvelity and monitor periodically during treatment. Monitor blood pressure, particularly in patients who receive the combination of bupropion and are receiving nicotine replacement.

**Activation of Mania/Hypomania:** Antidepressant treatment can precipitate a manic, mixed, or hypomanic episode. The risk appears to be increased in patients with bipolar disorder or who have risk factors for bipolar disorder. Prior to initiating Auvelity, screen patients for a history of bipolar disorder and the presence of risk factors for bipolar disorder (e.g., family history of bipolar disorder, suicide, or depression). Auvelity is not approved for use in treating bipolar disorder.

**Psychosis and Other Neuropsychiatric Reactions:** Auvelity contains bupropion and dextromethorphan. Depressed patients treated with bupropion have had a variety of neuropsychiatric signs and symptoms, including delusions, hallucinations, psychosis, concentration disturbance, paranoia, and confusion. In some cases, these symptoms abated upon dose reduction and/or withdrawal of treatment. Dextromethorphan overdose can cause toxic psychosis, stupor, coma, and hyperexcitability.

Because the risks of neuropsychiatric reactions are dose-related, screen patients for use of other bupropion- or dextromethorphan-containing products prior to initiating Auvelity. If concomitant use of Auvelity with other bupropion- or dextromethorphan-containing products is clinically warranted, monitor patients for neuropsychiatric reactions and instruct patients to contact a healthcare provider if such reactions occur.

**Angle-Closure Glaucoma:** The pupillary dilation that occurs following use of many antidepressants, including Auvelity, may trigger an angle closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy. Avoid use of antidepressants, including Auvelity, in patients with untreated anatomically narrow angles.
Ready for a new way to treat MDD?

Discover what makes Auvelity different and be the first to know when it is available for your patients. Visit Auvelity.com/HCP

Dopaminergic Drugs: Concomitant use with Auvelity can result in central nervous system toxicity. Use Auvelity with caution.

USE IN SPECIFIC POPULATIONS

Lactation: Because of the potential for neurotoxicity, advise patients that breastfeeding is not recommended during treatment with Auvelity and for 5 days following final dose.

Renal Impairment: Dosage adjustment is recommended in patients with moderate renal impairment (eGFR 30 to 59 mL/minute/1.73 m²). Auvelity is not recommended in patients with severe renal impairment (eGFR 15 to 29 mL/minute/1.73 m²).

Hepatic Impairment: Auvelity is not recommended in patients with severe hepatic impairment.

ADVERSE REACTIONS

Most common adverse reactions (≥5% and twice the rate of placebo): dizziness (16%), headache (8%), diarrhea (7%), somnolence (7%), dry mouth (6%), sexual dysfunction (6%), and hyperhidrosis (5%).

Please see Brief Summary of Prescribing Information on the following pages, including Boxed Warning for suicidal thoughts and behaviors.

AUVELITY™ (dextromethorphan Hbr-bupropion HCl) extended-release tablets, for oral use

Brief Summary of Prescribing Information
Before prescribing AUVELITY, please see full prescribing information, including boxed warning.

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS
See full prescribing information for complete boxed warning.

- Antidepressants increased risk of suicidal thoughts and behaviors in pediatric and young adult patients in short-term studies.
- Closely monitor all antidepressant-treated patients for clinical worsening, and emergence of suicidal thoughts and behaviors.
- AUVELITY is not approved for use in pediatric patients.

INDICATIONS AND USAGE
AUVELITY is indicated for the treatment of major depressive disorder (MDD) in adults.

CONTRAINDICATIONS
AUVELITY is contraindicated in patients:
- with a seizure disorder
- with a current or prior diagnosis of bulimia or anorexia nervosa as a higher incidence of seizures was observed in such patients treated with the immediate release formulation of bupropion
- undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs.
- taking, or within 14 days of stopping, MAOIs due to the risk of serious and possibly fatal interactions, including hypertensive crisis.

Starting AUVELITY in a patient treated with reversible MAOIs such as linezolid or intravenous methylene blue is contraindicated.

- with known hypersensitivity to bupropion, dextromethorphan, or other components of AUVELITY. Anaphylactic / anaphylactoid reactions and Stevens-Johnson syndrome have been reported with bupropion. Arthralgia, myalgia, fever with rash, and other serum sickness-like symptoms suggestive of delayed hypersensitivity have also been reported with bupropion.

WARNINGS AND PRECAUTIONS
Suicidal Thoughts and Behaviors in Adolescents and Young Adults
In pooled analyses of placebo-controlled trials of antidepressant drugs (SSRIs and other antidepressant classes) that included approximately 77,000 adult patients and 4,500 pediatric patients, the incidence of suicidal thoughts and behaviors in antidepressant-treated patients age 24 years and younger was greater than in placebo-treated patients. There was considerable variation in risk of suicidal thoughts and behaviors among drugs, but there was an increased risk identified in young patients for most drugs studied. There were differences in absolute risk of suicidal thoughts and behaviors across the different indications, with the highest incidence in patients with MDD. The drug-placebo differences in the number of cases of suicidal thoughts and behaviors per 1000 patients treated are provided in Table 1.

Table 1: Risk Differences of the Number of Patients of Suicidal Thoughts and Behavior in the Pooled Placebo-Controlled Trials of Antidepressants in Pediatric* and Adult Patients

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Drug-Placebo Difference in Number of Patients of Suicidal Thoughts or Behaviors per 1000 Patients Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18 years</td>
<td>Increases Compared to Placebo</td>
</tr>
<tr>
<td>14 additional patients</td>
<td></td>
</tr>
<tr>
<td>18-24 years</td>
<td>5 additional patients</td>
</tr>
<tr>
<td>25-64 years</td>
<td>Decreases Compared to Placebo</td>
</tr>
<tr>
<td>1 fewer patient</td>
<td></td>
</tr>
<tr>
<td>≥65 years</td>
<td>6 fewer patients</td>
</tr>
</tbody>
</table>

* AUVELITY is not approved for use in pediatric patients.

It is unknown whether the risk of suicidal thoughts and behaviors in children, adolescents, and young adults extends to longer-term use, i.e., beyond four months. However, there is substantial evidence from placebo-controlled maintenance studies in adults with MDD that antidepressants delay the recurrence of depression and that depression itself is a risk factor for suicidal thoughts and behaviors.

Monitor all antidepressant-treated patients for any indication for clinical worsening and emergence of suicidal thoughts and behaviors, especially during the initial few months of drug therapy, and at times of dosage changes. Counsel family members or caregivers of patients to monitor for changes in behavior and to alert the healthcare provider. Consider changing the therapeutic regimen, including possibly discontinuing AUVELITY, in patients whose depression is persistently worse, or who are experiencing emergent suicidal thoughts or behaviors.

Seizure
Bupropion, a component of AUVELITY, can cause seizure. The risk of seizure with bupropion is dose-related.

When a bupropion hydrochloride (HCl) sustained-release tablet was dosed up to 300 mg per day (approximately 1.5 times the maximum recommended daily dosage of AUVELITY), the incidence of seizure was approximately 0.1% (1/1,000) and increased to approximately 0.4% (4/1,000) at the maximum recommended dosage for the sustained-release tablet of 400 mg per day (approximately 2 times the maximum recommended daily dosage of AUVELITY).

The risk of seizures is also related to patient factors, clinical situations, and concomitant medications that lower the seizure threshold. Consider these risks before initiating treatment with AUVELITY. AUVELITY is contraindicated in patients with a seizure disorder, current or prior diagnosis of anorexia nervosa or bulimia, or undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs. The following conditions may also increase the risk of seizure: severe head injury; arteriovenous malformation; CNS tumor or CNS infection; severe stroke; concomitant use of other medications that lower the seizure threshold (e.g., other bupropion products, antipsychotics, tricylic antidepressants, theophylline, and systemic corticosteroids); metabolic disorders (e.g., hyperglycemia, hypocalcemia, severe hepatic impairment, and hypoglycemia); use of illicit drugs (e.g., cocaine); or abuse or misuse of prescription drugs such as CNS stimulants. Additional predisposing conditions include diabetes mellitus treated with oral hypoglycemic drugs or insulin; use of anorectic drugs; and excessive use of alcohol, benzodiazepines, sedative/hypnotics, or opiates.

Because the risk of seizure with bupropion is dose-related, screen patients for use of other bupropion-containing products prior to initiating AUVELITY. If concomitant use of AUVELITY with other bupropion-containing products is clinically warranted, inform patients of the risk.

Discontinue AUVELITY and do not restart treatment if the patient experiences a seizure.

Increased Blood Pressure and Hypertension
AUVELITY contains bupropion, which can cause elevated blood pressure and hypertension. The risk of hypertension is increased if AUVELITY is used concomitantly with MAOIs or other drugs that increase dopaminergic or noradrenergic activity. Assess blood pressure prior to initiating treatment, and periodically monitor blood pressure during treatment with AUVELITY.

Activation of Mania/Hypomania
Antidepressant treatment can precipitate a manic, mixed, or hypomanic episode. The risk appears to be increased in patients with bipolar disorder or who have risk factors for bipolar disorder.

Prior to initiating AUVELITY, screen patients for a history of bipolar disorder and the presence of risk factors for bipolar disorder (e.g., family history of bipolar disorder, suicide, or depression). AUVELITY is not approved for use in treating bipolar depression.

Psychosis and Other Neuropsychiatric Reactions
AUVELITY contains bupropion and dextromethorphan. Depressed patients treated with bupropion have had a variety of neurophysiologic signs and symptoms, including delusions, hallucinations, psychosis, concentration disturbance, paranoia, and confusion. Some of these patients had a diagnosis of bipolar disorder. In some cases, these symptoms abated upon dose reduction and/or withdrawal of treatment. Dextromethorphan overdose can cause toxic psychosis, stupor, coma, and hyperexcitability.

Because the risks of neuropsychiatric reactions are dose-related, screen patients for use of other bupropion- or dextromethorphan-containing products prior to initiating AUVELITY. If concomitant use of AUVELITY with other bupropion- or dextromethorphan-containing products is clinically warranted, monitor patients for neuropsychiatric reactions and instruct patients to contact a healthcare provider if such reactions occur.

Angle-Closure Glaucoma
The pupillary dilation that occurs following use of many antidepressant drugs including AUVELITY may trigger an angle-closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy. Avoid use of antidepressants, including AUVELITY, in patients with untreated anatomically narrow angles.

Dizziness
AUVELITY may cause dizziness. In controlled studies of AUVELITY, 14% of patients receiving AUVELITY and 6% of patients on placebo experienced dizziness. Take precautions to reduce the risk of falls, particularly for patients with motor impairment affecting gait or those with a history of falls. Caution patients about operating hazardous machinery, including motor vehicles, until they are reasonably certain that AUVELITY therapy does not affect them adversely.

Serotonin Syndrome
AUVELITY contains dextromethorphan. Concomitant use of AUVELITY with SSRIs or tricyclic antidepressants may cause serotonin syndrome, a potentially life-threatening condition with changes including altered mental status, hypertension, restlessness, myoclonus, hyperthermia, hyperreflexia, diaphoresis, shivering, and tremor.

Prior to initiating AUVELITY, screen patients for use of other dextromethorphan-containing products. If concomitant use of AUVELITY with other serotonergic drugs is clinically warranted, inform patients of the increased risk for serotonin syndrome and monitor for symptoms. Discontinue AUVELITY and/or concomitant serotonergic drug(s) immediately if the above symptoms occur and initiate supportive symptomatic treatment.

Embryo-Fetal Toxicity
Based on animal studies, AUVELITY may cause fetal harm when administered during pregnancy. In developmental toxicity studies in rats and rabbits, when a combination of dextromethorphan/quinidine was given to pregnant animals, fetal malformations (rabbis) and embryolethality were demonstrated in offspring. Neurotoxicity findings were observed in juvenile rats treated with a combination of dextromethorphan/quinidine on postnatal day (PND) 7, which corresponds to the third trimester of gestation through the first few months of life and may extend through the first three years of life in humans. The separate effect of dextromethorphan on developmental toxicity at the recommended clinical dose is unclear.

Discontinue treatment in pregnant females and advise the patient about the potential risk to a fetus. Use alternative treatment for females who are planning to become pregnant.

ADVERSE REACTIONS
Clinical Trials Experience
AUVELITY was evaluated for safety in a total of 23,144 patients with MDD or another indication from four studies (two 6-week studies in MDD, one 6-week study in another indication, and one long-term study in MDD and another indication). One 6-week study in MDD employed placebo as a control arm. Two 6-week studies, one in MDD and one in another indication, employed bupropion as a control arm. In the patients treated with AUVELITY in the long-term study (n=576), 597 received at least 6 months of treatment, and 110 received at least 12 months of treatment. The data below are based on the 6-week, placebo-controlled study in which either AUVELITY (n=162) or placebo (n=164) was administered twice daily to patients with MDD (Study 1).

Comparison of the incidence of anorgasmia was not statistically significant between the groups. AUVELITY and placebo were equally effective in improving the mean change from baseline in Montgomery-Asberg Depression Rating Scale (MADRS) score at Week 6 (AUVELITY: −7.2, placebo: −7.7).

Table 2: Incidence of Treatment-Emergent Adverse Reactions in ≥5% of Patients Treated with AUVELITY and More Frequently than in Patients Treated with Placebo in a 6-Week Study (Study 1)

<table>
<thead>
<tr>
<th>Reaction</th>
<th>AUVELITY (n=162)</th>
<th>Placebo (n=164)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Headache</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Migraine</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2%</td>
<td>1%</td>
</tr>
</tbody>
</table>

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**Adverse Reactions Leading to Discontinuation**

In the 6-week placebo-controlled study, 4% of patients treated with AUVELITY and 0% of placebo-treated patients discontinued participation due to adverse reactions. The adverse reaction that led to study discontinuation in 2% of patients treated with AUVELITY was anxiety (2%).

**Most Common Adverse Reactions**

In the 6-week placebo-controlled clinical study, the most common (incidence ≥5%) for AUVELITY and more than twice as frequent as placebo) adverse reactions were dizziness (16%), headache (8%), diarrhea (7%), somnolence (7%), dry mouth (6%), sexual dysfunction (6%), and hyperhidrosis (5%).

Table 2: Adverse Reactions Occurring in ≥2% of Adult Patients with MDD Treated with AUVELITY and More Frequently than in Patients Treated with Placebo in a 6-Week Placebo-Controlled Study (Study 1)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>AUVELITY (N=162)</th>
<th>Placebo (N=164)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>Nausea</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>Headache</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Somnolence</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Sexual dysfunction†</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Anxiety</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Constipation</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Insomnia</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Fatigue‡</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Paroesthesia†</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

*Sexual dysfunction includes orgasm abnormal, erectile dysfunction, libido decreased, anorgasmia

†Fatigue includes fatigue, lethargy

Paroesthesia includes paraesthesia, hypoesthesia

**DRUG INTERACTIONS**

**Table 3: Clinically Important Drug Interactions with AUVELITY**

<table>
<thead>
<tr>
<th>Monamine Oxidase Inhibitors (MAOIs)</th>
<th>Clinical Impact</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUVELITY is contraindicated in patients taking MAOIs (including MAOIs such as linezolid or intravenous methylene blue) or in patients who have taken MAOIs within the preceding 14 days. Allow at least 14 days after stopping AUVELITY before starting an MAOI.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Serotonergic Drugs**

<table>
<thead>
<tr>
<th>Clinical Impact</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concomitant use of AUVELITY with other serotonergic drugs increases the risk of serotonin syndrome.</td>
<td></td>
</tr>
</tbody>
</table>

**Drugs that Lower Seizure Threshold**

<table>
<thead>
<tr>
<th>Clinical Impact</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUVELITY contains bupropion which can cause seizure. Co-administration with other drugs that lower seizure threshold may increase risk of seizure.</td>
<td></td>
</tr>
</tbody>
</table>

**Intervention**

Use caution when administering AUVELITY concomitantly with drugs that lower the seizure threshold. Discontinue AUVELITY and do not restart treatment if the patient experiences a seizure.

**Strong Inhibitors of CYP2D6**

<table>
<thead>
<tr>
<th>Clinical Impact</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concomitant use of AUVELITY with strong CYP2D6 inhibitors increases plasma concentrations of dextromethorphan.</td>
<td></td>
</tr>
</tbody>
</table>

**Intervention**

Dosage adjustment is necessary when AUVELITY is coadministered with strong inhibitors of CYP2D6. Monitor patients for adverse reactions potentially attributable to dextromethorphan, such as somnolence and dizziness.

**Strong Inducers of CYP2B6**

<table>
<thead>
<tr>
<th>Clinical Impact</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concomitant use of AUVELITY with strong CYP2B6 inducers decreases plasma concentrations of dextromethorphan and bupropion and may decrease efficacy of AUVELITY.</td>
<td></td>
</tr>
</tbody>
</table>

**Drugs Metabolized by CYP2D6**

<table>
<thead>
<tr>
<th>Clinical Impact</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coadministration of AUVELITY with drugs that are metabolized by CYP2D6 can increase the exposures of drugs that are substrates of CYP2D6.</td>
<td></td>
</tr>
</tbody>
</table>

**Drugs that Require Metabolic Activation by CYP2D6**

Drugs that require metabolic activation by CYP2D6 to be effective could have reduced efficacy when administered concomitantly with AUVELITY.

**Intervention**

When used concomitantly with AUVELITY, it may be necessary to decrease the dose of CYP2D6 substrates, particularly for drugs with a narrow therapeutic index.

**Drugs that Require Activation by CYP2D6**

Patients treated concomitantly with AUVELITY may require increased doses of drugs that require activation by CYP2D6 to be effective.

**Digoxin**

<table>
<thead>
<tr>
<th>Clinical Impact</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coadministration of AUVELITY with digoxin may decrease plasma digoxin levels.</td>
<td></td>
</tr>
</tbody>
</table>

**Dopaminergic Drugs**

<table>
<thead>
<tr>
<th>Clinical Impact</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS toxicity was reported when bupropion was co-administered with levodopa or amantadine. Adverse reactions have included restlessness, agitation, tremor, ataxia, gait disturbance, vertigo, and dizziness.</td>
<td></td>
</tr>
</tbody>
</table>

**Intervention**

Use caution when administering AUVELITY concomitantly with dopaminergic drugs.

**Alcohol**

<table>
<thead>
<tr>
<th>Clinical Impact</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUVELITY contains bupropion which can increase adverse neurobehavioral events or reduce alcohol tolerance.</td>
<td></td>
</tr>
</tbody>
</table>

**Intervention**

The consumption of alcohol should be minimized or avoided during treatment with AUVELITY.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Pregnancy Exposure Registry**

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antidepressants, including AUVELITY, during pregnancy. Healthcare providers are encouraged to register patients by contacting the National Pregnancy Registry for Antidepressants at 1-866-961-2368 or online at: https://womensmentalhealth.org/research/pregnancyregistry/antidepressants/

**Risk Summary**

Based on animal studies, AUVELITY may cause fetal harm when administered during pregnancy. AUVELITY is not recommended during pregnancy if a female becomes pregnant while being treated with AUVELITY, discontinue treatment and counsel the patient about the potential risk to a fetus.

**Clinical Considerations**

Disease-Associated Maternal and/or Embryo/Fetal Risk

Women who discontinued antidepressants during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressants. Consider the risks to the mother of untreated depression and potential effects on the fetus when discontinuing or changing treatment with antidepressant medications during pregnancy and postpartum.

**Lactation**

**Risk Summary**

Because of the potential for neurotoxicity, advise patients that breast-feeding is not recommended during treatment with AUVELITY and for 5 days following final dose.

**Renal Impairment**

Dosage adjustment of AUVELITY is recommended in patients with moderate renal impairment (eGFR 30 to 59 mL/minute/1.73 m²). The pharmacokinetics of AUVELITY have not been evaluated in patients with severe renal impairment. AUVELITY is not recommended in patients with severe renal impairment (eGFR 16 to 29 mL/minute/1.73 m²).

**Hepatic Impairment**

No dose adjustment of AUVELITY is recommended in patients with mild (Child-Pugh A) or moderate hepatic impairment (Child-Pugh B). The pharmacokinetics of AUVELITY have not been evaluated in patients with severe hepatic impairment (Child-Pugh C). AUVELITY is not recommended in patients with severe hepatic impairment.

**CYP2D6 Poor Metabolizers**

Dosage adjustment is recommended in patients known to be poor CYP2D6 metabolizers because these patients have higher dextromethorphan concentrations than extensive/intermediate CYP2D6 metabolizers.

**AUV HCP BS 08/2022**

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In This Issue

What do football and psychiatry have in common? For starters, there are “wins” in both. In football, scoring a touchdown requires players to have tenacity, perseverance, concentration, and the willingness to forge ahead despite the human obstacles in their way. Similarly, to help patients achieve treatment success, clinicians use their earned wisdom and a sense of determination to overcome various treatment obstacles, including complicated diagnoses and insurance hassles.

Both football players and psychiatrists require good game plans, but they also need to read the field and know when—and how—to zig instead of zag. Such is the case when unexpected adverse effects pop up. Sharon Packer, MD, shares the story of one patient who had such an issue, and how she needed to pass the ball to a specialist. Similarly, both clinicians and football players need to engage in good defensive mechanisms in order to win. In psychiatry, that might mean monitoring electrocardiograms for some patients who have been prescribed lithium, as David N. Osser, MD, shares in this month’s Bipolar Update column. And let’s not forget the importance of cheering. In this issue’s Special Report, we look at issues in patient empowerment and patient education, as “cheering” and supporting patients is an important path to success.

Here at Psychiatric Times®, we continue to cheer you, our reader, by providing you with the tools, tips, and information from cover to cover to make your game plans successful.

Mike Hennessy, Jr.
President and CEO
MJH Life Sciences®

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Publisher’s Note

Cheerleading and Game Plans

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From the Editor

Is Science Drifting Into the Dark Ages?

John J. Miller, MD  Editor in Chief  Dr Miller is Medical Director, Brain Health, Exeter, New Hampshire; Editor in Chief, Psychiatric Times™; Chief Scientific Officer, Seacoast Mental Health Center, Exeter; Consulting Psychiatrist, Seacoast Hospital, Exeter; Consulting Psychiatrist, Insight Meditation Society, Barre, Massachusetts.

With each passing year, to my confusion and dismay, the edifice of science that I was drawn to as a young boy—and in which I remain immersed and inspired—feels to be slowly dismantling. During my elementary school years, my parents fostered and supported my love for the natural sciences. Christmas presents included a microscope, a chemistry set, a Radio Shack kit to build electronic devices, camping supplies, and scuba gear along with a certification course. In high school, I took every science class that was available, and I loved mathematics. Yes, I am a proud science nerd through and through. My passion to understand the natural world exploded as I pursued my BS in biochemistry with a certification course. In high school, I took every science class that was available, and I loved mathematics. Yes, I am a proud science nerd through and through. My passion to understand the natural world exploded as I pursued my BS in biochemistry with a certification course. 

Historical Perspective

The Age of Sail was the time period from the mid-16th through mid-19th century, during which sailing ships were dominant for exploration, global trade, and warfare. Because expeditions often lasted many months and fruit and vegetables quickly spoiled, the sailors on these vessels went without. As a result, approximately 50% of all sailors (or 2 million individuals) died due to scurvy.

In 1747, Scotsman James Lind, a Royal Navy surgeon on the ship HMS Salisbury, observed the onset of scurvy after 2 months at sea. Lind had researched the topic and hypothesized that scurvy was due to a dietary deficiency. With scurry cases on the rise, Lind performed what is believed to be the first randomized clinical trial. He randomly assigned 12 sailors with scurvy into pairs, and all were provided the same food, fluids, and care. Each pair was then given 1 of 6 possible treatments daily: seawater, cider, vinegar, dilute sulfuric acid, plant extracts, or 2 oranges and a lemon. The 2 sailors who received oranges and lemons recovered rapidly, but none of the other 10 sailors improved. Lind published his results in 1753. It wasn’t until a year after Lind’s death that the British Admiralty made lemon juice compulsory on all ships in 1795. In 1928, vitamin C deficiency was determined to be the etiology of scurvy.

Paradigm-Changing Discoveries

One of the remarkable qualities of Homo sapiens is how quickly we adapt to advancing technologies and how just as quickly we forget what life was like before their existence. There are many paradigm-changing discoveries that originally humbled and excited us that we now tend to take for granted (Table). These transformative discoveries are given little thought, much like our entitled expectation that the sun should rise and set every day and that our planet should be able to always provide for our increasing consumption of food and energy.

Due to many of those scientific advances, quality of life increased, and the average life expectancy in the United States increased from aged 39 years in 1860 to 79 years in 2020 (Figure). Two items stand out as likely having made the largest contribution in the doubling of our life expectancy: vaccines and antibiotics, both of which emerged from centuries of good science.

Vaccines and COVID-19

Remarkably, over the past 20 years in the United States, there has been an erosion of public opinion and trust that the pharmaceutical industry has applied the best science to develop these vaccines and antibiotics. This phenomenon has become all too apparent by our country’s divisiveness and tribalism during the COVID-19 pandemic, during which a large subset of our population opined the vaccines were malevolent manipulations by the deep state or camouflaged vehicles to inject dangerous materials into our bodies. Additionally, conspiracy theories claiming that...
the COVID-19 pandemic was a fabrication for various rogue reasons still abound. Sadly, the Center for Disease Control became the victim of political attacks. Predictably, the slow but steady accumulation of knowledge and subsequent recommendations was misconstrued as incompetence and misinformation. Pseudo-experts continue to share their unscientific opinions and prophesy to vulnerable populations who want to believe them, likely resulting in great harm.

Climate Change

As any good therapist will affirm, denial is a powerful defense. Despite an overwhelming database of peer-reviewed published literature and expert consensus on climate change resulting from human behaviors causing global warming, a large segment of the United States population does not believe climate change is real.

Cautionary publications in the 1990s warned us about the potentially catastrophic consequences to the Earth if the rapidly rising temperature on the planet was left unchecked. An Inconvenient Truth, published in 2006 by former Vice President Al Gore, raised public awareness and created a lot of debate, but eventually the concern diminished. A 2021 article in Academic Medicine noted, “In 2019, an international multidisciplinary Lancet collaboration concluded that climate change poses unacceptable threats to the health of public health threats of the 21st century and a defining modifier of the global burden of disease.”

Over the past 5 years, the United States has experienced the beginnings of these climate change impacts and weather patterns: drought, flooding, large forest fires, oppressive heat waves, and more powerful hurricanes. Despite these regularly occurring climate change-related events and virtually unanimous consensus among scientists that human behavior is the primary cause, a significant number of people still do not believe it.

Conclusion

The citrus fruit of the 17th century is our COVID-19 vaccine. However, unlike Lind who had limited resources to perform the first randomized clinical trial in medical history, the pharmaceutical industry excelled at designing, performing, analyzing, and reporting the results of extremely well-designed double-blind, placebo-controlled clinical trials. Such has been the case for all the COVID-19 vaccines now available to us. The cog in the wheel of treatment today is misinformation and lack of trust in the institutions of medicine, peer-reviewed published literature, the CDC, and pharmaceutical research. Regrettably, the many snake oil salespeople often win the trust of the vulnerable.

Science is, and will always be, a work in progress. The beauty of science is that it is constructed slowly and steadily on the foundation of all that has been discovered and established by committed individuals during the years, decades, and centuries preceding this moment in time. Thus, science endures despite the hysteria, whines, and selfish agendas that attack and defy it.

Regrettably, history has taught us that the knowledge and dogma of established science does not impact society in a linear fashion. Through the past 2000 years, the tides of changing agendas have moved science back and forth from a luminous ally facilitating tremendous advances and improvements for humanity to the dark recesses of a deep and forbidden cave.

Ideally, science should be apolitical. The knowledge gained should be applied to improve the quality of life of all citizens of the Earth and inform us in the care and health of our planet. If only the policy makers would evolve with the knowledge that science provides to facilitate the health and wellness of our planet, our children, our grandchildren, and all generations to come. It saddens me that this is not currently the case.

Alas, I have no answers or recommendations regarding how to elevate science so it may shine its bright light in the service of our species and our planet. I do have a deep and existential concern that science is drifting into the dark ages.

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Nevertheless, patients, families, and clinicians must still make critical health care decisions, such as a patient’s determination to engage in or refuse treatment, often with urgency and limited information. The COVID-19 pandemic has compounded the obstacles physicians commonly face in gaining patient acceptance of treatment and psychiatric referral; physicians often encounter exacerbated suspicion, mistrust, and emotional isolation even in individuals who do not suffer from neuropsychiatric impairment.

So, what happens when the law inappropriately holds individuals with neuropsychiatric impairment to legal standards that are discordant with the behavioral reality of their conditions, functioning as a barrier to acquiring the information needed to make a life-altering decision? Specifically, when do we decide to provide care for a patient with neuropsychiatric impairment if the Health Insurance Portability and Accountability Act of 1996 (HIPAA) is of substantial concern? HIPAA is a federal law that requires the creation and maintenance of national standards to protect sensitive patient health information from being disclosed without that patient’s consent or knowledge. HIPAA justifiably protects patient information and privacy, but it can also potentially be implemented or interpreted in a manner that compromises the provision of treatment.

Hence, it is vital to remember that there is ample room for physicians to use clinical discretion and professional judgment under HIPAA’s exceptions.

**CASE EXAMPLE** Mrs Martinez is a woman aged about 55 years presenting with severe depression and symptoms of psychosis, including paranoia. She has become substantially impaired by fears and fixed ideas, isolating herself and unable to work. Her husband is caring for her, but her employer requires a physician’s letter to preserve her job and acquire disability-related reasonable accommodations. The physician, who treats the patient and her entire family, learns of Mrs Martinez’s condition from her parents. However, Mrs Martinez refuses to see the physician. What can be done for the patient and her family while complying with HIPAA requirements? HIPAA aims to protect patient privacy, yet here its operationalization might inhibit care provision, leading to a worse health outcome.

**Discussion**

Given other circumstances, the patient presumably would have made a deliberate decision by weighing the benefit of timely disclosure against the loss of privacy or control of her personal health information. This measured decision-making process is vital in making decisions that affect one’s health, safety, and well-being. However, neuropsychiatric impairment can diminish this faculty. For example, depression can warp one’s perception of reality to such an intense degree that all hope seems lost, and psychosis can profoundly disconnect one from reality. Thus each, respectively, impairs decision-making.

This mismatch between the law’s presumptions of rationality and the behavioral manifestations of neuropsychiatric impairments is most readily on view with forms of severe mental illness, and it creates a perennial hazard that situational factors exacerbate—as seen during the COVID-19 pandemic. Friction between the law’s fundamental assumptions and the clinical realities of neuropsychiatric impairments leads to countless delayed treatments, prolonged illnesses, unnecessary incarcerations, and even death.

**Fortunately, there is a practical workaround under HIPAA that provides for limited disclosure.** Per 45 C.F.R. § 164.510(b)(3), if disclosure cannot practically be provided because of the individual’s incapacity or an emergency circumstance, the covered entity may, in the exercise of professional judgment, determine whether the disclosure is in the best interests of the individual and, if so, disclose only the protected health information that is directly relevant to the person’s involvement with the individual’s care.

In this case example, the treating physician correctly informed Mrs Martinez’s parents that they could provide information regarding her condition. However, the physician also told the parents that she could not, in return, provide information or share observations of the patient. With the information provided by the parents, the physician drafted a letter that provided Mrs Martinez’s employer with the information required to preserve her job and support eligibility for disability-related accommodations. Since the physician’s letter was necessary to maintain the patient’s insurance coverage for treatment, it fits under the exception to the consent requirement.

Mrs Martinez eventually met with an independent medical examiner, who confirmed her disability and suggested various treatment options with family support. The examiner herself could not provide treatment, just as the treating physician could only give a factual account of her clinical impressions, not an objective disability evaluation. Moreover, although the examiner’s evaluation in this context was not therapy, it ultimately served a therapeutic purpose: After this positive experience with the independent medical examiner, who met with Mrs Martinez in her home office, Mrs Martinez consented to treatment with a psychiatrist.

This resolution highlights how a patient can more readily accept psychiatric treatment in a supportive context and obviates the need for a health care proxy or guardianship, which both pose risks to a vulnerable patient’s agency. Despite neuropsychiatric impairment, clinicians can find ways to respect their patients’ autonomy, dignity, and privacy to provide them with both disability accommodations and treatment. With the pandemic intensifying patients’ usual reasons for resisting psychiatric referral—such as fear of stigma, perceived threats to self-esteem or privacy, and lack of understanding of emotional concomitants of medical illness—physicians can best facilitate such referrals with empathy, clear communication, and reassurance of continued medical care.

**Concluding Thoughts**

The case study poses a difficult trade-off, balancing the patient’s right to self-determination versus the duty to provide care. However, when neuropsychiatric impairment diminishes the capacity for rational decision-making, the presumption of reasonability must give way. Clinicians can nonetheless respect a patient’s dignity and agency in these instances while concurrently preserving the patient’s well-being. Overbroad interpretations and applications of HIPAA need not outweigh ethical duties to patients. Through sound professional judgment and an understanding of HIPAA exceptions to the consent requirement, we can help patients heal and return to a state of mind where they can truly exercise their autonomy, maintain their dignity, and ensure their right to privacy.

Mr Larrauri is a member of the National Alliance on Mental Illness Board of Directors in Arlington, Virginia. Dr Bursztajn is a faculty member at Harvard Medical School, and a practicing psychiatrist in Cambridge, Massachusetts, with a longstanding interest in decisions making under conditions of trauma and uncertainty. Dr Stein is executive director of the Harvard Law School Project on Disability in Cambridge, Massachusetts.

**References**

Tales From the Clinic: The Art of Psychiatry
Series Editor Nidal Moukaddam, MD, PhD

In this installment of Tales From the Clinic: The Art of Psychiatry, we examine the case of posttraumatic stress disorder (PTSD) in the setting of homelessness and substance use. Most homeless individuals report experiencing significant trauma at some point in their lives. This discussion examines the correlation between trauma and homelessness, and touches on vicarious trauma endured by treating physicians as well. It is easy to fall into negative perceptions of patients with homelessness, trauma, and substance use. Successful treatment hinges on remaining humane in perspective and viewing such cases as very high in comorbidity and needing additional psychosocial support.

“"I’m Homeless and I Have PTSD”
Treatment Considerations

Julie Williams, MD

CASE STUDY
"Ms Harris" is a middle-aged woman with a history of PTSD and alcohol use disorders who is currently receiving substance use treatment at a homeless shelter. She is engaged in a substance treatment program for the first time in her life.

Ms Harris was raped by an uncle at age 12 and advised by her mother to keep the incident a secret. After the rape, she started struggling with academic performance and she stopped attending school at age 16. She married at age 19 and quickly had 2 children. Her husband was physically and emotionally abusive in their marriage. She started drinking alcohol to cope with the abuse. She divorced her husband after 20 years of marriage when her youngest child turned 18. She received a small financial settlement after the divorce but had exhausted her savings after 3 years. She was unable to sustain employment because of her alcohol use and discomfort interacting with strangers. During this time, her alcohol use escalated and her relationship with her children became strained. After exhausting her financial resources, Ms Harris experienced significant alcohol withdrawal and was admitted to the medical unit for treatment. She was evicted from her apartment for nonpayment while inpatient and she was subsequently discharged to a local shelter and substance use rehabilitation program.

Ms Harris is seen by a psychiatrist after completing the first 30 days of her sobriety. She is visibly anxious with significant psychomotor agitation. She reports difficulty with sleep initiation as well as sleep maintenance. She finds interacting with her peers uncomfortable and isolates herself when possible.

During the visit, she reports significant irritability, primarily triggered by her peers and loud noises. She also reports having taken escitalopram in the past with poor effect.

Psychological Considerations
Distrust of others is a well-known symptom of PTSD. Childhood maltreatment—including emotional abuse, emotional neglect, physical abuse, physical neglect, and sexual abuse—is also associated with increased distrust as well as interpersonal threat perception in adulthood. This often presents a challenge to the therapeutic alliance. Engaging in the principles of trauma-informed care is critical to both establishing trust and avoiding retraumatization.

During Ms Harris’ initial visit, she is reminded that her participation in the appointment is voluntary and confidential. Prior to giving a trauma history, she is advised that while she may be asked about broad categories of abuse, she can decline to answer any questions that make her uncomfortable and request that no trauma history be obtained at the initial visit. She is invited to provide any details that she does feel comfortable discussing, but is reassured that she will not be asked to divulge any painful details of her past. Ms Harris discusses that she had been sexually abused as a child and physically abused as an adult, but declines to provide further details during the first few visits.

Substance Use
During the initial interview, Ms Harris has some ambivalence about her alcohol use. While she understands that her use had escalated to an unhealthy level, she also reports that it was her primary means of coping with her anxiety. Without it, she reports a significant escalation of her symptoms. She worries about her ability to tolerate a substance use treatment program.

Ms Harris is not alone in her difficulties with alcohol use. Some studies show the prevalence of alcohol dependence in homeless patients to be upward of 55%, and similar rates of drug dependency. In emergency departments, rates of substance use were significantly higher, sometimes doubled, in homeless patients compared with those who did not report homelessness. While there are many hypotheses surrounding these findings, one cannot ignore the influence of trauma. Substance use disorders and PTSD often co-occur, with 1 study finding that up to 46% of patients with PTSD also meet criteria for a substance use disorder. Successful treatment of both disorders simultaneously is critical for patient improvement.

Pharmacologic Considerations
Ms Harris is initially started on sertraline for PTSD. Given her distrust of others and perceived failure of another selective serotonin reuptake inhibitor, considerable time is spent in psychoeducation surrounding the role and effects of medications in her treatment plan. She is also started on naltrexone for alcohol use disorder. Trazodone is used for sleep initiation difficulties.

In subsequent visits, the patient reveals that she is having nightmares surrounding the physical abuse by her ex-husband. She reports that the dream frequency has not changed with the initiation of her other medications. Doxazosin is added. Although more research is needed in...
patients with comorbid PTSD and alcohol use disorder, doxazosin has had some promising results when studying these illnesses separately.6

Other treatment options aimed at addressing her anxiety, such as hydroxyzine and gabapentin, are discussed but declined by the patient because of a fear of daytime sedation. Topiramate is also discussed, as it has shown promise in patients with cooccurring PTSD and alcohol use disorder, although additional studies are needed.7 Ultimately, this medication is also omitted from the treatment plan because of the potential for cognitive deficits, which could impair her ability to participate fully in her substance use treatment program.

Progress
The shelter helps Ms Harris remain adherent with her medications with frequent reminders and scheduled medication times. She participates in cognitive behavioral therapy (CBT)-based substance use treatment classes as well as group and individual therapy. She engages in prolonged exposure for her traumas. Over many weeks, Ms Harris begins to trust her psychiatrist and engage in more peer support activities. Her emotional and physical reactivity improve. With the help of the shelter’s case manager, Ms Harris is able to obtain work in the retail industry. As graduation approaches, she becomes more anxious. Her psychiatrist initiates a CBT-based model aimed at addressing her cognitive distortions surrounding her ability to be successful outside a structured setting. Ms Harris graduates from the substance treatment program and moves into an apartment.

She is followed closely by her psychiatrist after graduation. Immediately following her transition out of the shelter, the patient reports a recurrence of anxiety and sleep disturbance. In addition, she reports a relapse after being offered alcohol by a well-meaning neighbor. While initially struggling with significant shame and guilt, the patient is able to abstain from further use. Trazodone is transiently increased, and Ms Harris continues to address her anxiety in therapy with positive effect.

After many months, Ms Harris becomes romantically involved with a neighbor at her apartment complex. She reports an improvement in her anxiety and continued sobriety in the weeks following the start of their relationship. She is lost to follow-up.

Setbacks
Ms Harris returns to the clinic after 1 year. She reports that her boyfriend did not support her use of psychiatric medications and advised her to stop them. He soon became increasingly emotionally abusive and the patient relapsed on alcohol. Two weeks ago, he sexually assaulted her after she declined to have intercourse. She has not told anyone about the assault but ended the relationship. She reports feeling fearful because the man still lives in her apartment complex.

Her psychiatrist provides emotional support while encouraging the patient to report the assault to the police and consider seeking a restraining order in accordance with state law. She is also obtained to use urgent gynecologic care and is given information about a local family violence shelter. While the patient declines to report the incident to the police or seek resources from the family violence shelter, she agrees to seek gynecologic care. The patient restarts her medications and is able to taper off alcohol as an outpatient.

Concluding Thoughts
Working with homeless patients can be exceedingly rewarding. Patients such as Ms Harris can and do improve at a remarkable rate with the appropriate support and treatment. However, there are also challenges facing psychiatrists who work with homeless patients (Figure), notably vicarious trauma. Psychiatrists in this area are inherently exposed to personal reports of trauma repeatedly throughout the day. One study in Canada showed rates of PTSD in helping professions related to homelessness were 2 to 3 times higher than what were found in other frontline professions such as police work and emergency services.4 Therefore, it is imperative that those working with this patient population actively engage in their personal wellness and ensure they are receiving support from their institution.
Boxed Warnings:

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

• Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric and young adults in short-term studies. Closely monitor all antidepressant-treated patients for clinical worsening, and for emergence of suicidal thoughts and behaviors. The safety and effectiveness of CAPLYTA have not been established in pediatric patients.

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

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

• Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis, including stroke and transient ischemic attack. See Boxed Warning to the left.

• Neuroleptic Malignant Syndrome, which is a potentially fatal reaction. Signs and symptoms include hyperpyrexia, muscle rigidity, delirium, autonomic instability, elevated creatinine phosphokinase, myoglobinuria (and/or rhabdomyolysis), and acute renal failure. Manage with immediate discontinuation of CAPLYTA and provide intensive symptomatic treatment and monitoring.

• Tardive Dyskinesia (TD), a syndrome of potentially irreversible, dyskinetic, and involuntary movements which may increase as the duration of treatment and total cumulative dose increases. The syndrome can develop after a relatively brief treatment period, even at low doses, or after treatment discontinuation. Given these considerations, CAPLYTA should be prescribed in a manner most likely to reduce the risk of TD. Discontinue CAPLYTA if clinically appropriate.

• Metabolic Changes, including hyperglycemia, diabetes mellitus, dyslipidemia, and weight gain. Hyperglycemia, in some cases extreme and associated with ketoacidosis, hyperosmolar coma or death, has been reported in patients treated with antipsychotics. Measure weight and assess fasting plasma glucose and lipids when initiating CAPLYTA and monitor periodically during long-term treatment.

Help your patients get relief from their bipolar depression with titration-free, once-daily CAPLYTA 42 mg
Choose CAPLYTA
for a broad range of adults with bipolar depression

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

*Based on the Montgomery-Asberg Depression Rating Scale (MADRS) total score at week 6.

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

Orthostatic Hypotension and Syncope. Monitor heart rate and blood pressure and warn patients with known cardiovascular or cerebrovascular disease. Orthostatic vital signs should be monitored in patients who are vulnerable to hypotension.

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

Seizures. Use CAPLYTA cautiously in patients with a history of seizures or with conditions that lower seizure threshold.

Potential for Cognitive and Motor Impairment. Advise patients to use caution when operating machinery or motor vehicles until they know how CAPLYTA affects them.

Body Temperature Dysregulation. Use CAPLYTA with caution in patients who may experience conditions that may increase core body temperature such as strenuous exercise, extreme heat, dehydration, or concomitant anticholinergics.

Dysphagia. Use CAPLYTA with caution in patients at risk for aspiration.

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

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

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

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

References: 1. CAPLYTA prescribing information, 2021.

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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 (median duration of 10 weeks), largely in patients taking typical antipsychotic drugs, revealed a risk of death in drug-treated patients of 1.6 to 1.7 times that 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%, compared to a rate of about 2.6% in placebo-treated patients. Although the causes of death were varied, most of the deaths appeared to be cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. CAPLYTA is not approved for the treatment of patients with dementia-related psychosis.

Suicidal Thoughts and Behaviors

Antidepressants increased the risk of suicidal thoughts and behaviors in children, adolescents, and young adults compared to placebo during short-term treatment. This risk was consistent for various classes and diverse regimens of antidepressants and was noted in the absence of a difference in baseline risk of suicidal symptoms between treatment groups.

CAPLYTA is not approved for use in pediatric patients.

It is unknown whether the risk of suicidal thoughts and behaviors in children, adolescents, and young adults exposed to antidepressants in clinical trials is the same as the risk of suicidal thoughts and behaviors in paediatric patients with schizophrenia. Because of the potential risk of suicidal thoughts and behaviors in children, adolescents, and adults receiving antipsychotic drugs, monitor all antidepressant-treated patients for suicidal thoughts and behaviors. If suicidal thoughts or behavior emerge, or worsen, the drug should be discontinued abruptly, and alternative management measures should be initiated.

CAPLYTA is not approved for use in pediatric patients.

DOSAGE AND ADMINISTRATION

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

Dosage in Elderly Patients: No de novo use of CAPLYTA is recommended in elderly patients based on a post hoc analysis of effects on cognitive function in patients age 65 or older in clinical trials.

Dosage Recommendations for Concomitant Use with CYP3A4 Inducers and Moderate or Strong CYP3A4 Inhibitors - Concomitant use of CAPLYTA with a CYP3A4 inhibitor may increase plasma concentrations of lumateperone. Monitor patients carefully for adverse reactions when using in combination with a CYP3A4 inhibitor, including ritonavir, clarithromycin, and nefazodone.

CAPLYTA is not approved for use in pediatric patients.

INDICATIONS AND USAGE

CAPLYTA is indicated for the treatment of schizophrenia in adults and depressive episodes associated with bipolar I or II disorder (bipolar depression) in adults, as monotherapy and as adjunctive therapy with lithium or valproate.

CONTRAINDICATIONS

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

WARRANTIES 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 (median duration of 10 weeks), largely in patients taking typical antipsychotic drugs, revealed a risk of death in drug-treated patients of 1.6 to 1.7 times that 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%, compared to a rate of about 2.6% in placebo-treated patients. Although the causes of death were varied, most of the deaths appeared to be cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. CAPLYTA is not approved for the treatment of patients with dementia-related psychosis.

Increased Mortality in Elderly Patients with Schizophrenia: Elderly patients with a known history of depression, dementia, Parkinson's disease, or stroke have a higher risk of mortality compared to younger patients with schizophrenia.

CAPLYTA is not approved for use in pediatric patients.

Falls:

Patients with dementia-related psychosis treated with antipsychotics have an increased risk of falls. Monitor patients carefully for signs and symptoms of falls.

CAPLYTA is not approved for use in pediatric patients.

Cerebrovascular and/or withdrawal symptoms, including agitation, hypertonia, hypertensive crisis, and/or intracranial hypertension, can occur in patients treated with antipsychotic drugs. A negative family history may be an independent risk factor for antipsychotic-induced extrapyramidal and/or withdrawal symptoms, including agitation, hypertonia, hypertensive crisis, and/or intracranial hypertension. All antipsychotic drugs may cause extrapyramidal and/or withdrawal symptoms, including agitation, hypertonia, hypertensive crisis, and/or intracranial hypertension, in patients whose depression is persistently worse, or who are experiencing suicidal thoughts or behaviors.

Central Nervous System Effects

Neuroleptic Malignant Syndrome: Neuroleptic Malignant Syndrome (NMS), a potentially fatal syndrome, has been reported in association with administration of antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, delirium, and autonomic instability. Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. If NMS is suspected, immediately discontinue CAPLYTA and provide intensive symptomatic treatment and monitoring.

Tardive Dyskinesia: Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with antipsychotic drugs. The risk of tardive dyskinesia and the likelihood that it will become irreversible increase with the duration of treatment and the cumulative dose. The syndrome can develop after a relatively brief treatment period, even at low doses. It may also occur after discontinuation of treatment.

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

Given these considerations, CAPLYTA should be prescribed in a manner most likely to reduce the risk of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients: 1) who suffer from a chronic illness that may be expected to respond to antipsychotic drugs; and 2) who have shown a satisfactory response to antipsychotic drugs in the treatment of their illness in the dosage and duration of treatment required to control their illness. It may be necessary to alternate antipsychotic drugs to delay the appearance of tardive dyskinesia.

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

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

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

Schizophrenia - In pooled data from short-term (4- to 6-week), placebo-controlled trials of adult patients with schizophrenia, mean changes from baseline and the proportion of patients with shifts from normal to greater than normal levels of fasting glucose in patients treated with CAPLYTA were similar to those in patients treated with placebo.

In an uncontrolled open-label trial of CAPLYTA for up to 1 year in patients with stable schizophrenia, the percentages of patients with a shift from normal to high were 2.4% and 2.6% at baseline and 4.7% of patients with normal hemoglobin A1c (>5.8%) at baseline developed levels ≥5.8% post-baseline. Bipolar Disorder - In data from short-term (6-week), placebo-controlled monotherapy and adjunctive therapy bipolar depression trials, mean changes from baseline and the proportion of patients with shifts to higher levels of fasting total cholesterol and triglycerides were similar in patients treated with CAPLYTA and placebo.

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

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

CAPLYTA is not approved for use in pediatric patients.

Pediatric Use:

CAPLYTA is not approved for use in pediatric patients.

No dosage adjustment is recommended for patients with mild hepatic impairment (Child-Pugh A).

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Elderly patients with dementia-related psychosis treated with antipsychotics have an increased risk of falls. Monitor patients carefully for signs and symptoms of falls.

CAPLYTA is not approved for use in pediatric patients.

No dosage adjustment is recommended for patients with mild hepatic impairment (Child-Pugh A).

Distributed by Intra-Cellular Therapies, Inc.

Elderly patients with dementia-related psychosis treated with antipsychotics have an increased risk of falls. Monitor patients carefully for signs and symptoms of falls.

CAPLYTA is not approved for use in pediatric patients.
Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Antipsychotic drugs, including CAPLYTA, should be used cautiously in patients at risk for aspiration.

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

The safety of CAPLYTA has been evaluated in placebo-controlled clinical trials in 2684 adult patients with schizophrenia or bipolar disorder. In a total of 562 CAPLYTA-exposed patients who had at least 6 months of exposure and 108 had at least 1 year of exposure at the 42 mg dose of CAPLYTA. Schizophrenia - The following findings are based on the pooled short-term (4- to 6-week), placebo-controlled trials of CAPLYTA. The rates of adverse reactions were generally similar across trials with CAPLYTA and placebo. Treatment-emergent adverse reactions, which occurred in ≥5% of patients treated with placebo or with CAPLYTA at a rate greater than placebo are as follows: (incidence of at least 2% in at least 1 placebo group or a rate greater than placebo). Adverse reactions associated with CAPLYTA (incidence of at least 2% in patients exposed to CAPLYTA and greater than placebo) were as follows: (incidence reaction is followed by percentage of patients treated with CAPLYTA 42 mg: n=208; patients treated with placebo (n=122) in parentheses). Bipolar disorder - treatment-emergent adverse reactions associated with CAPLYTA were administered at a daily dose of 42 mg (n=86).

There was no single adverse reaction leading to discontinuation that occurred at a rate of ≥2% in CAPLYTA-treated patients. The most common adverse reactions (incidence of at least 5% of patients exposed to CAPLYTA and greater than twice the rate of placebo) were somnolence/sedation, dizziness, nausea, and dry mouth.

Adverse reactions associated with CAPLYTA (incidence of at least 2% in patients exposed to CAPLYTA and greater than placebo) were as follows: (incidence reaction is followed by percentage of patients treated with CAPLYTA 42 mg: n=237; patients treated with placebo (n=150) in parentheses). Schizophrenia - Treatment-emergent adverse reactions occurred in ≥5% of patients treated with CAPLYTA and placebo (incidence reaction is followed by percentage of patients treated with placebo), nausea, sedation, somnolence, fatigue, tremor, weight gain, dizziness, dry mouth, vomiting, and insomnia. Treatment-emergent adverse reactions occurring at a rate greater than placebo were as follows: (incidence reaction is followed by percentage of patients treated with CAPLYTA 42 mg: n=117; patients treated with placebo (n=75) in parentheses). Schizophrenia - Treatment-emergent adverse reactions occurring at a rate >2% in CAPLYTA-treated patients were as follows: (incidence reaction is followed by percentage of patients treated with CAPLYTA 42 mg: n=177 and patients treated with placebo (n=117) in parentheses). Schizophrenia - Treatment-emergent adverse reactions occurring at a rate >2% in CAPLYTA-treated patients were as follows: (incidence reaction is followed by percentage of patients treated with placebo). Schizophrenia - Treatment-emergent adverse reactions occurring at a rate >2% in CAPLYTA-treated patients were as follows: (incidence reaction is followed by percentage of patients treated with placebo). Schizophrenia - Treatment-emergent adverse reactions occurring at a rate >2% in CAPLYTA-treated patients were as follows: (incidence reaction is followed by percentage of patients treated with placebo).

Data - Animal Data: Pregnancy: Pregnancy Exposure Registry - Information on calcium, magnesium, phosphorus, potassium, sodium, and other electrolytes were similar to those in patients treated with placebo. Schizophrenia - In an uncontrolled open-label trial of CAPLYTA for up to 6 months in patients with bipolar depression, the proportion of patients achieving a ≥50% reduction in the Montgomery-Asberg Depression Rating Scale (MADRS) at endpoint from baseline was significantly greater for CAPLYTA than for placebo. Schizophrenia - The most common adverse reactions (incidence of at least 5% of patients exposed to placebo) and greater than twice the rate of placebo) were somnolence/sedation, dizziness, nausea, and dry mouth.

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THE QUEST: Nepal Lets You Reach for the Majesty of the Summit

Lloyd I. Sederer, MD

It’s 40 degrees below zero. You are breathing thin air with one-fourth the sea level of oxygen. You haven’t slept in 2 days. Every step you take feels like your legs are encased in concrete. You are flanked by 100-m crevasses.

Is this some form of torture? Maybe the photo is of a climber frozen in place since 1962? Might this be payment due for buying all that nonreturnable gear at Eastern Mountain Sports? Or perhaps it is a Himalayan scene from a forthcoming Hangover film?

It’s worse. Because it’s no joke to climb to Everest Base Camp (17,500 ft) in Khumbu, Nepal, after having flown to remote Lukla airport (9,400 ft) on what looks like an old toy plane. Then there is the climb to camps 1, 2, 3, and 4 (the last at 23,000 ft)—the way stations for those whose minds are set on ascending to the summit (29,032 ft).

Let’s start in the capital city of Nepal—Kathmandu (1,460 ft, population roughly 846,000, without its “urban” sprawl)—as did the climbers in THE QUEST: Nepal. Tourism dominates your first day as your local guide, fluent in English, herds you to a gargantuan market of narrow, serpentine streets, lined by every stripe of merchant. Hindu and Buddhist shrines are features of the tour, some restored or under reconstruction after the earthquake (7.8 on the Richter scale) in 2015. Never sidestepped on the itinerary is the cremation, some restored or under reconstruction after the earthquake, open 24 h/d, where followers of Hinduism burn their dead and sweep their remains into a tributary of the Ganges River.

This film beautifully uses Kathmandu to mentally transport you, like the climbers, into the journey ahead. You mix with its people, pay respect to its historic shrines, witness its dead being cremated in the open air, and realize that you are very far from home, in many ways.

I was in Kathmandu in 1995, beginning a trek to the base camp of Annapurna (13,550 ft), the 10th-highest mountain in the world (26,545 ft), which is as deadly as Everest to those seeking its summit (not me). The people of Nepal radiate a warmth and welcoming that is now uncommon. This immersion into Kathmandu will be the most significant Nepalese experience that most tourists—and they are legion—will have. THE QUEST offers a tender and detailed account of the city—a gift, and no less than the icy sites ahead.

The Everest quest then moves on to Lukla. THE QUEST concentrates its cameras on individuals, especially Ryan Waters (the American lead climber), touching lightly on his climbing team, the Nepalese Sherpas, and the guides. Waters is tall, fair, lean, and collegiate looking, radiating keen interest and humanity; only later will you see his unwavering grit, when the going gets impossible by most human standards. It is hard to read him—to appreciate what has driven him to this over-the-top and potentially fatal adventure. About 300 climbers have died on Everest; we see the cairns marking their burial sites along the ascent.

There is not much tech talk in the film’s portrayals (not that I wanted it). We see the extraordinary mountaineering equipment and the massive support staff, but they do not take center stage. I had a group of 10 assisting my 4-person, nontechnical climb. There is not a word in the film about funding THE QUEST, which surely was a bargain considering the cost of an Elon Musk SpaceX rocket launch.

We march the white mountain from one harrowing place to another, as if beside Waters and his team. This is as close a perspective of the mountain and him as is possible. Watching Waters persevere with a smile begs the question: Why would an individual subject himself to what otherwise appears enormously punishing?

Metaphor and simile are useful in considering this question. Everest is a massive mountain scraping the sky, cold and unforgiving, lording its dominance over the likes of us. Climbing it would be like a heavyweight boxing championship: Glory to the winner of the battle, although the mountain will not feel the punches—you will. Climbing the mountain must also be an exercise in seeking to dominate your fearful, less-than-invincible self.

The amygdala is an almond-shaped nerve bundle, barely an inch long, within the brain’s temporal lobes. It is the origin of our fears (from “fight or flight” to intimacy). The mountain challenges the amygdala, as the amygdala challenges the mountain. Talk about David and Goliath.

A quotidian life could be transformed by the majesty of the summit. There would be pain, but not the variety that debilitates—rather, a pain that runs from head to toe and shouts that you are truly alive. No doubt about it.

The loneliness that pervades our lives, which is as much a health risk as 15 cigarettes a day, would evaporate—diffuse into the clouds. Because in extreme climbing, the climber has 2 intimate and ardent bonds. One is to the fearsome giant, the mountain to be tamed, the yin to your yang, and the source—ironically—of the juice in your blood. The other is the extraordinary attachment to your teammates, leaning into danger as you are—the eyes, ears, and desire beyond your own. It is this type of attachment the military trains soldiers so “no one is left behind.” You are bathed, if you will, in closeness otherwise almost unimaginable.

Reaching THE QUEST summit seems anticlimactic, but it is a rare moment. The film ends in triumph, richly deserved. Yet, it is still less than we can comprehend. If you ever meet a mountaineer, offer him or her a drink in exchange for a glimpse into their soul.


Dr. Sederer is a contributing writer for Psychiatric Times™, and a psychiatrist, public health doctor, and nonfiction author.
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Book Review

Christianity and Psychiatry

Reviewed by Renato D. Alarcón, MD, MPH

Christianity and Psychiatry is the third of a book series focused on several angles of the religion-psychiatry equation, published in the last 3 years and edited, practically, by the same team of scholars. These features confer high academic quality and a homogeneous set of perspectives on the topic of Christianity and its many links with psychiatry throughout centuries. The 2 previous volumes dealt with Islamophobia and anti-Semitism as human/behavioral/emotional attitudes. Christianity may not engender a similar magnitude of negative responses, but, perhaps for the very same reason, its connections with psychiatry exhibit a larger variety of fronts.

This was the objective pursued by the 4 editors (from Harvard Medical School, Medical College of Wisconsin, Duke Medical Center, and King’s College London)—asking a total of 31 authors (23 from the United States, 3 from Canada, 3 from the United Kingdom, and 1 each from Scotland and the Netherlands) to contribute 21 chapters. As the foreword and the introduction state, the book addresses different levels of faith and tradition versus medical and scientific knowledge, their antagonisms and controversies, and their integration and mutuality. A panoramic and detailed analysis of the book’s content led this reviewer to formulate a catalogue of 5 areas explored throughout the chapters—areas sometimes clearly delineated, and other times, inevitably mixed because of their complexities. It is not an isolating compartmentalization because the connections emerge almost spontaneously; nevertheless, I will describe and explore them as orderly as I can in an attempt to systematize the impressive richness of the reading material. The first 3 areas are history, clinical practice, and education, while the last 2 examine implicit contradictions (not from or between the authors, but owned by the topics themselves) and some conceptual or formal, although not necessarily formidable absences.

History

The historical focus touches authoritatively on many chapters. Some readers may feel that the first one, titled “The fraught history of Psychiatry and Christianity,” would be sufficient with its impressive deployment of information from biblical sources to lucid perspectives during the Middle Ages and accomplishments of legendary figures like Augustine of Hippo, Baxter, Tuke, Brigham, Charcot, Janet, and William James throughout the past 6 centuries.

The questioning of divinely inspired behaviors of Old Testament heroes as possible psychiatric syndromes also started a long time ago (chapter 3). It seems that the stigma of mental conditions (including self-stigma) has always existed (chapters 2 and 14). We learn about the Christian origins of Alcoholics Anonymous (chapter 11) and the inclusion of “care of the soul” envisioned and clearly spelled out by Johann Christian Reil (the creator of the name, “psychiatry,” for our field) in 1808 (chapter 16).

Clinical Practice

Clinical practice encompasses diagnostic and treatment/management actions, all reflecting well-defined objectives and a positively directed pragmatism. The historical detection of stigma, mostly among Christian (“charismatic,” “authoritarian”) communities and churches since ancient times, set the stage for the materialization of faith-inspired healing (chapter 2). In turn, religion and God became a source of resilience and adaptability, particularly among young people (chapter 3). The distinction between psychotic symptoms and spiritual phenomena led to early conceptualizations of clinical processes later named spectra, an important contemporary nosological term that anticipated the great potential of a mutually understanding collaboration between clinicians (chapter 3). In the therapeutic field, the progressive Christian view allowed the acceptance of “folk healing,” a strongly culture-based treatment approach that undoubtedly used components of support, empathy, encouragement, and inspiration in non- or nominally Christian patients (chapters 1, 18, and 19).

The book addresses different levels of faith and tradition versus medical and scientific knowledge.

The polemics between conservative (mostly Protestant) and liberal Christians generated anger and confusion, but also channeled the first elements of the contemporary concept of Liberation Theology (chapter 19). As important, one learns of the prophet Muhammad’s protective attitude toward Christians (chapter 19) and considers the history of ideological and temperamen-
Christian psychiatry:

1. Its celebration of reconciliation as the driving force of emotional recovery and of life as a quest for existential meaning—all preceding Viktor Frankl’s existentialism and logotherapy (chapter 4)

2. Shared decision-making and a value-based practice (Fulford’s legacy) that confers to psychiatry the role of a “normative practice approach” compatible with a communitarian approach in social philosophy and ethics—the latter in the route of principles like beneficence, mercifulness, charity, altruism, hope, and trust (chapter 12)

3. The study of relational phenomena that, beyond “levelism” and contextualization, focus on intersubjectivity and the existence of “the third” outside of exclusively dyadic doctor-patient and teaching-audience perspectives (chapter 16)—a wise anticipation of the “otherness” phenomenon that is so profoundly relevant in today’s psychiatry and psychotherapy

Contradictions

A book of this nature must also examine old and current contradictions in the field of the so-called Christian psychiatry to assert truth and objectivity. The polemics between Freudian pronouncements about religion in general—and Christianity and its churches, in particular—are mentioned several times, somehow personifying it in their exchanges and Freud’s final rupture with Jung. Beyond that, the Christian vision reflects yesterday and today’s many confrontations between psychology and psychiatry (chapter 12). Differing interpretations of the same clinical phenomena, a frequent reality among clinicians, occur equally among theologians discussing the religious/spiritual meaning of psychopathological behaviors (chapter 4). Last but not least, contradictions are recognized and discussed within and between Christian churches in their consideration of psychiatric symptoms, syndromes, and diseases, and—perhaps more profoundly—between Jewish (the first Christians in history) and Black Christians (chapters 14 and 19).

Absences

Finally, a reviewer must point out absences, omissions, and even excesses in the work being read—quasi-criticisms that may be quite personal or questionable. A broad, panoramic view of the religious/spiritual perspective as a strong component of old and contemporary cultural psychiatry seems to be missing; some may say that the whole book is sort of a treaty on the topic, but an ontological precision in the form of a brief chapter may have helped. The role of the family is mentioned many times, but lacks focus and clear meaning—again, from a cultural (not only Christian) perspective. Theoretical speculations were unavoidable on occasions, and simplistic-looking explanations (i.e., slow breathing settling autonomic nervous system activation) may have been so probably due to space reasons.

In short, this volume is a fascinating incursion into a field that everybody talks about, but few examine in depth. It offers excellent historical reviews, valuable clinical experiences, selected didactic pearls, and, in its last 3 chapters, meaningful autobiographies of psychiatrists from different religious backgrounds sharing a common work that is full of essentially human ingredients: psychiatry. As the last paragraphs point out, this perspective assists patients of all religious persuasions and viewpoints, encouraging them and their psychiatrists to integrate faith with the rest of their lives. This book will also help psychiatrists and other mental health professionals “remain aware of (their) blind spots and needs for both God and science,” reaching, in turn, “a view of truth that is evidence-based, clinically relevant, and informed by the wisdom of Christianity and its fellow traditions.”

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If you are of a certain age, you will recall the saying: “Doctor knows best.” After the civil rights era and the social justice advances of various groups, including patients, the saying became more like: “Both doctors and patients know best.” Actually, it is even broader than that when you go beyond an individual private practice office to treating more complex patients with serious illnesses. Then we have something like: “The team know best.”

Following doctors’ orders in psychiatry has always been a challenge. Stigma, denial, confusion, and misinformation often contributed to the reluctance, or nonadherence, of patients. That was what led me early on in my career to try to empower patients. What follows is what a colleague remembered from sitting in on my patient interactions in the early 1980s:

“Dr Moffic was a coleader with the patient in the room. He found ways to ask his patient what the patient thought about his/her treatment. This may sound like a small thing, but it was rare. . . . I had never heard another psychiatrist ask his patient what medication they thought would work best. . . . He was empowering his patients to have a voice in their treatment and medication. I believed this partnership approach also improved his patient’s [adherence] with taking their medication.”

This caseworker, Herb Bateman, started and empowered one of the earliest patient peer services.

As patients with severe mental illness are involved with their families in one way or another, families were brought in with the permission of the patient because their positive expression was therapeutic and they needed to be empowered too.

Education had similar feedback loops. Though we psychiatrists were usually the most thoroughly educated and had much to teach, we had to try to follow what other clinicians wanted to learn and also what they could teach. This feedback was especially important in recognizing and reducing structural racism in our clinics.

Back in the early 1990s, I was asked to be the medical...
The Importance of Avoiding Implicit Bias in Advocating for Patients

Natasha Massoudi, MD, MPH; Agata Piotrowska, BS; Kayla Behbahani, DO

The tele-geropsychiatry new patient consultation appointment started. The patient and his wife were on camera. The patient was able to answer most of the interview questions himself, with his wife chiming in intermittently. The patient was a very pleasant man living with Parkinson disease. We talked about where the patient and his wife live, their children, the patient’s time in the military, and the state of his mood. Then I asked about eating and sleeping and started the review of medications. Here we go, I said to myself.

The consult was a referral from the patient’s primary care physician noting anxiety and that “wife requests a pill for patient’s clonazepam 1.0 mg qhs.” The consult mentioned that clonazepam was the only medication to assist with the patient’s mood and sleep. It also mentioned that the primary care physician had recommended trazodone but that the prescription was never filled. Naturally, I thought about clonazepam and the fall risk for the patient—an older gentleman with Parkinson disease—and about how clonazepam is the “only medication that assists the patient,” according to the consult. I was eager to talk with the patient and his wife and curious about whether there might be pushback when discussing the adverse effects of such a medication, especially in a patient with Parkinson disease.

I was prepared to discuss the risks and benefits of using clonazepam at this dose in an individual with dizziness and falls, compounded by a neurodegenerative disease. Then came a natural pause—one of the moments in the psychiatric interview that can often be just a moment to hold space with the patient.

“He used to thrash in his sleep,” the patient’s wife said. “Thrash?” I asked. “Yes,” she said. “Could you tell me a little bit more?” I asked.

The patient’s wife then described years in which the patient would become agitated during the night, moving his legs and arms and sometimes striking his wife during these episodes. The only medication that the patient had used over the last 12 years was clonazepam. When he trialed quetiapine, the thrashing got worse.

I thought to myself: Thrashing…in someone with Parkinson disease…got worse with quetiapine…Could this in fact be rapid eye movement sleep behavior disorder (RBD)? I quickly went to UpToDate and searched for “treatment” and “first line: clonazepam 0.5 to 1.0 mg qhs.” Then came the “ah-ha” moment.

The patient and his family were never told the actual medical name for “thrashing.” They were never told that the clonazepam was to lessen these episodes. There was no documentation of this diagnosis anywhere in the patient’s direct access chart. It was through digging back 11 years in a remote medical chart and finding one neurology note that said—albeit in 3 letters—“RBD,” with no subsequent explanation, that I realized this was what the patient was experiencing. Could it be true?

This was not about benzodiazepines. It was not about overdose or misuse of the drug. It was about the first-line FDA-approved drug for RBD—and the only one that worked for this patient. RBD is a disorder in which patients act out their dreams, which is commonly seen with comorbid Parkinson disease.” This diagnosis was never discussed with the patient and his family, who were also never given a diagnosis to explain the years of sleep disruption. It never made it into the patient’s formal diagnosis list, so it never got carried forward on his problem list.

I immediately wondered how many times this patient must have not been listened to because his wife was asking only for clonazepam. What would have happened if his wife had never mentioned Thrashing during sleep in this patient encounter? This certainly could have gone very differently.

Today, when doctors are targeted for irresponsible prescribing practices, how many physicians are hesitant to prescribe what turns out to be the first-line treatment for a legitimate medical condition? Ultimately, that is where the buck stops. Sometimes this is due to preconceived notions or scenarios we often play out in our head prior to engaging with patients. Sometimes it is because we do not dig deep enough into medical charts and then make assumptions. And then, there is a staunch reminder that the patient’s story is the center of the encounter. We need to keep an open mind about the patient’s narrative and ensure that it is what remains front and center.

Our own implicit biases come into play at times whether we like it or not, especially when it comes to frequently controversial medications. If we do not ask, if we do not explore, and if we do not engage in those moments of holding space with patients, our biases can cloud our judgment and divert patient care in very different directions than intended. Listening to patients, asking them questions, and maintaining an open mind throughout the conversation can be key not only to preventing our implicit biases from taking over, but also to providing more effective patient care.

Dr Massoudi is a PGY2 psychiatry resident at Nova Southeastern University College of Medicine/Bay Pines VA Healthcare System. Ms Piotrowska is a medical student at Nova Southeastern University College of Medicine. Dr Behbahani is an associate training director of the general adult psychiatry residency program and geriatric psychiatry site director at Nova Southeastern University College of Medicine.

References

Dr Moffie is an award-winning psychiatrist who has specialized in the cultural and ethical aspects of psychiatry. A prolific writer and speaker, he received the one-time designation of Hero of Public Psychiatry from the Assembly of the American Psychiatric Association in 2002. He is an advocate for mental health issues related to climate change, understanding the cultural and ethical implications of medication overuse or misuse of the drug. It was about the first-line FDA-approved drug for RBD—and the only one that worked for this patient.
The data is clear: We should expect an increasing number of transgender and gender diverse (TGD) youth presenting to our practices over the coming years.1 We must ask ourselves: Are we prepared to treat these patients and their families with the most affirming, evidence-based treatment available?2

Case Example For discussion purposes, consider a prototypical case of “Bar,” an 11-year-old child who presents to your office accompanied by his parents. Bar was assigned female at birth but recently began identifying with “he/him” pronouns; he is scared to face impending puberty. Bar’s father informs you that he is afraid Bar will be “bullied for being gay.”

Supporting the Patient and Their Family
Recent qualitative studies suggest that the caregivers’ response and adjustment to their TGD child’s identity development is critical to the child’s mental health.3 An integrative family therapy approach should affirm and support the TGD child in an equal partnership between the caregivers and the child.4 Addressing attunement and attachment is important for the family system, as there is likely longstanding intergenerational trauma from adoption of rigid, binary gender norms.5 Families should prioritize building psychosocial support for, and affirming the gender identity of, the TGD child, rather than focus on worries like “Is this my fault?” “What went wrong?” or “Is this just a phase?” The family may express grief due to the loss of an expected future they associated with the assigned sex of a transitioning child.6 Distress tolerance and interpersonal relationship dynamics can be tested during a gender transition; as a result, many with gender dysphoria may be misdiagnosed with personality disorders.7 Dialectical behavioral therapy is a good therapeutic option for these patients.8 It is important that group therapy options provide affirming environments for transgender group members. This includes the facilitator’s role modeling of appropriate usage of pronouns and chosen names during therapy sessions.

Disclosing a shared identity with a patient can aid the therapeutic alliance by displaying understanding and empathy for the patient’s experience, which can facilitate trust and reciprocity.9,10 It is vital that providers reflect on whether self-disclosure is being done with the intent of improving patient care, and peer supervision around this can be of value. Psychiatrists should model inclusive environments to their TGD patients within their offices and clinical spaces.11 Patients and their families should feel safe to give feedback to the psychiatrist when they fail to produce an affirming patient experience.4 In these situations, the administrative response should be transparent and timely, and it should address the root cause of the issue. Psychiatrists should collaborate and advocate with the family and other community and mental health professionals, such as school psychologists and counselors, to create affirming environments within the child’s home and school life.12 It is imperative that work with TGD patients

<table>
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<th>TABLE 1. Recommended Psychoeducational Approach for Families of a Transgender or Gender-Diverse Child</th>
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<td><strong>Language</strong></td>
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involves ongoing feedback and participation from affected community members throughout the learning and healing process.¹⁴

To create a more affirming environment for a TGD child, psychiatrists should collaborate with the family, school, and community. For example, using noninvasive and empowering language can be a great first step in establishing not only a good environment, but also a therapeutic alliance. See Table 1 for more information, and the Sidebar on Page 39.

Psychiatric Terminology: Is the Field Doing Enough?
Gender Dysphoria and Its Significance in the TGD Community
Gender dysphoria is a term that originated within psychiatry. The DSM-5-TR defines gender dysphoria as “the psychological distress that results from an incongruence between one’s sex assigned at birth and one’s gender identity.” Gender euphoria is an accepted term used in the TGD community, as “the psychological distress that results from one’s gender-related incongruence.” Gender dysphoria and euphoria can result in higher rates of depression, anxiety, trauma and stress disorders, rumination, somatization, and suicidality in TGD individuals.¹⁵⁻²¹

The mismatch between a person’s self-identified gender and invalidated environments can occur within multiple domains, including online, home, school, athletic, employment, carceral, and health care settings.²²⁻²⁴ Access to affirming environments and health care improves mental health outcomes²⁵⁻²⁷; on the other hand, nonaffirming environments and barriers to health care increase disparities for TGD individuals.²⁸⁻³⁰ Due to recent attempts to criminalize evidence-based affirming health care for TGD individuals, psychiatrists should expect to see an increase in patients presenting with gender dysphoria in the near future.³¹

The Gender Minority Stress and Resilience Theory
The Gender Minority Stress and Resilience Theory describes the disparate impact of risk and protective factors on the experience of internalized (proximal) and external (distal) oppression in TGD communities.³² These stress and resilience factors combine with other forms of social identity–based discrimination, such as racism and socioeconomic disadvantage. Taken together, this intersectionality is responsible for the structural pathways leading to systemic health care inequities experienced by TGD community members (ie, social determinants of health).³³ Figure 2 provides more details on minority stress and resilience.

Minority stress models have been used to explain the increased risk for biological, psychological, and social health disparities observed in TGD communities. These biological factors include increased rates of cardiovascular disease and cancer-related outcomes, whereas psychological outcomes of minority stress include depression and suicidality.³⁴⁻³⁸ Among the TGD community, social disparities and structural disadvantages have been noted in increased rates of incarceration, housing instability, underinsurance, and risk behaviors, such as substance misuse as a negative coping mechanism.³⁷⁻³⁹⁻⁴¹

Conclusion of Case Example
You diagnose Barr with gender dysphoria and provide supportive psychotherapy throughout the social transition process. You present Barr with information regarding his local community center, where Barr becomes active in peer support and social activities. You provide educational resources to Barr’s parents, who join their local PFLAG (Parents, Families, and Friends of Lesbians and Gays) chapter to speak with other parents of TGD children. You discuss the changes in pronouns with Barr’s school psychologist and work with school administration to help develop strategies for Barr to express his gender authentically within the school’s policies.

After a year of treatment, although Barr feels more confident in his masculine gender expression, he reports ongoing depression due to expected changes with puberty. As a result, you refer Barr and his parents to a gender-affirming endocrinologist to discuss options regarding potential puberty suppression and timing.

Concluding Thoughts
Psychiatrists are in a unique position to empower their patients by recognizing and addressing key issues surrounding gender and sexuality. This includes the use of sensitive and inclusive language and assisting the field in adapting to ongoing evolution of community standards of care. Similarly, it is important to integrate transition and resocialization efforts with the patient’s family, community centers, and school professionals. Table 2 provides a list of potential resources to help in this

Figure 2 expands on this topic and gives examples of resilience, or protective factors, that moderate the effect of minority stress.⁴² Resilience factors include methods to create systemic and structural changes that increase the psychosocial support and affirming environments available to TGD individuals.⁴³ Additionally, TGD individuals can learn skills such as community building, advocacy, role modeling, and other expressions of pride, self-worth, and self-acceptance.

Concluding Thoughts
Psychiatrists are in a unique position to empower their patients by recognizing and addressing key issues surrounding gender and sexuality. This includes the use of sensitive and inclusive language and assisting the field in adapting to ongoing evolution of community standards of care. Similarly, it is important to integrate transition and resocialization efforts with the patient’s family, community centers, and school professionals. Table 2 provides a list of potential resources to help in this
endavor. Together, we can work to provide affirmative and evidence-based care for all youth, whether or not they identify within the gender binary.

Ms Rollán is a sixty-year medical student at the Universidad Católica de Cuyo, in Mendoza, Argentina. She aspires to become a neuropsychologist and to continue advocating through research and policymaking for the rights of transgender people.

Dr Leoni is a board-certified neuropsychologist and graduate student of social service at Fordham University, where they perform activism and research for the transgender community.

References
Psychiatrists Are Physicians First
Here’s Why This is Important

Sharon Packer, MD

Lilly” lived as well as she did, as long as she did, because the sun does not shine in SoHo. In New York City’s SoHo district, cast-iron constructions more than a century old cast long, dark shadows, like the black shadows in Batman comic books. Narrow alleyways separate back-to-back buildings, leaving almost no room for shafts of sunlight to seep in. Film noir—style shadows are abundant in that part of town, as they are in Batman’s fictional Gotham City, inspired by Manhattan’s cast shadows.

SoHo began as a manufacturing zone, where floor-through factories did not demand sunny cityscape views. Yet today’s SoHo is a fashionable area with little trace of its past. It housed my psychiatry practice for the last decade. When manufacturing left New York City, those large SoHo spaces turned into artists’ lofts, which then gave way to art galleries. Gradually, pricey designer boutiques replaced many galleries, and fashionably dressed shoppers and shop salespeople displaced artists.

Lilly was unlike other SoHo shop salespeople who wore unaffordable dress samples that turned them into breathing billboards. She was an apprentice jewelry designer at an established shop on Prince Street, a few blocks from my office. Even though she was only an intern and still a student, she had already amassed an impressive portfolio. She was wearing one of her creations when she arrived at my office for her first appointment—a little late, because passers-by had stopped her on the street to ask where she sold her unique brooches. Such was life in SoHo.

Lilly was referred by Fashion Institute of Technology (FIT) Student Health Services to resume treatment that had begun in grade school. When manufacturing left New York City, those large SoHo spaces turned into artists’ lofts, which then gave way to art galleries. Gradually, pricey cobblestone streets that paved those deep caverns created by cast-iron towers. To commute to FIT, she jumped on the N train at the Prince Street subway stop, half a block away. To travel to her job at the jewelry store—which offered course credit toward her jewelry-making certificate—she sped down Prince Street, located a short, shaded block from my office. She scheduled the earliest appointment available and then darted between the shadows, crossing narrow cobblestone streets that paved those deep caverns created by cast-iron towers. Upon return, she complained that her hands hurt, and that her fingers turned blue.

As her social anxiety subsided, she shared details about her early life in small-town Phoenicia, which was a few hours from Manhattan, geographically speaking, but light-years away on a cultural level. Lilly was forthcoming about her struggles in school and the fact that most of her family members lacked so much as a high school diploma, much less advanced degrees. Still, despite her dyslexia—or maybe because of it—Lilly created clever necklaces from cans that she scavenged near the Esopus Creek, where shabby trailer camps contrasted with picturesque waterfalls that attracted tourists.

Phoenicia was a simple place, known for camping and tubing and long stretches of tall, fragrant pine trees. There, Lilly’s mother tended garden at a vacation home owned by a well-to-do Brooklyn couple. Her father functioned as a live-in caretaker, allowing the family to live rent-free. Their basement apartment was drafty and cold in the winter, when the owners were away and the heat was off, but it was still better than the trailers that lined the riverbanks, according to Lilly.

Her family lived underground—no taxes, no voting—until Lilly applied for a state scholarship. But every weekend, her father packed his pick-up truck with a fresh supply of reported hostas, selling them to second-home owners. Lilly joked about weekenders’ willingness to pay outsized prices for minimal efforts needed to propagate common plants that grew in their shade garden. Eventually, Lilly’s father added her found-material brooches and bracelets to his hosta display. This caught the eye of an elderly tourist, who suggested that she create a portfolio and apply for a scholarship to FIT so she could hone her skills and prepare for a “real world” career. Lilly had never heard the word “portfolio” before, but she was impressed when she heard that both husband and wife were college professors. So, she followed their advice. She won a scholarship, thanks to this chance encounter. Her creations also impressed a jeweler in SoHo, who offered her an internship at his shop, with a chance to make jewelry from “real” metals, not just discarded metal cans.

At each appointment, Lilly shared more details of her day-to-day life. She made her way to work early each morning, exiting the tenement apartment she shared with an elderly aunt on Mulberry Street, located a short, shaded block from my office. She scheduled the earliest appointment available and then darted between the shadows, crossing narrow cobblestone streets that paved those deep caverns created by cast-iron towers. To commute to FIT, she jumped on the N train at the Prince Street subway stop, half a block away. To travel to her job at the jewelry store—which offered course credit toward her jewelry-making certificate—she sped down Prince Street in the opposite direction. Sometimes, she said, she headed for a hidden alley near Houston Street, where she studied at a library that was sheltered from public view but gave her a great angle from which to watch discreetly staged fashion shoots at the far end of the alley. Lilly did not resent her limited itinerary, for she found the New York City crowds too overwhelming, and she appreciated the predictability of a set schedule. And Lilly’s life was indeed predictable until something changed in late winter.

For Presidents’ Day weekend, a classmate invited her on a ski trip at an upstate resort—and that was when things started to shift. Embarrassed to admit that she could not afford a lift ticket, much less ski, Lilly sat on the sidelines for hours, near the snow-covered and sun-drenched trails. Upon return, she complained that her hands hurt, and that her fingers turned blue.

Lilly was describing Raynaud syndrome, which could worsen with vasoconstricting stimulants. Still, it seemed odd that such an adverse effect (AE) started so suddenly, after so many years on the same medication. Besides, she lived further north, where winters were far worse, yet she...
Psychosomatics

never previously had such symptoms in the cold. Then the clues started to fall into place. She also began experiencing fatigue once she sat outside on the slopes, which was equally strange, considering that stimulants are energizing and are sometimes used (illicitly) to combat fatigue.

I was unwilling to write these symptoms off to AEs, but I was also unwilling to continue a stimulant that could conceivably worsen Raynaud, especially since the medication offered minimal benefit for Lilly’s major dyslexia symptoms. So, we tapered her off the ADHD medication, but the pain in her fingers persisted—even though she was on SSRI, which can relieve Raynaud. It was time to see the primary care physician (PCP) to find other explanations for concomitant fatigue, Raynaud, and joint pain in a 20-year-old woman. I ordered basic labs and added an antinuclear antibody (ANA) test. Her PCP referred her to a rheumatologist when the ANA read a telling 1:360.

Lilly was still waiting for a specialist appointment when college graduation came around. By then, she had a solid job offer from the jewelry boutique that had hired her as an intern. Her family was ecstatic. To celebrate this unanticipated success, they scheduled a surprise family vacation, with plans to drive their battered old pick-up truck south and stay with relatives in Key West, Florida.

Sadly, the trip was not the celebration that had been intended, but it did start to explain her symptoms. While walking outside in the intense Florida sun, Lilly developed a raised, red rash on her nose, which sounded like the butterfly rash of lupus. Her joints hurt so much that she sidestepped the sub-sun, which was equally strange, considering that stimulants are energizing and are sometimes used (illicitly) to combat fatigue.

For patients 6 years and older with Attention Deficit Hyperactivity Disorder

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CNS stimulants, including DYANAVEL XR, other amphetamine-containing products, and methylphenidate, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy.

DYANAVEL XR (amphetamine) is contraindicated
• in patients known to be hypersensitive to amphetamine, or other components of DYANAVEL XR. Hypersensitivity reactions, such as angioedema and anaphylactic reactions, have been reported with other amphetamines
• in patients taking monoamine oxidase inhibitors (MAOIs), or within 14 days of stopping MAOIs, because of increased risk of hypertensive crisis
• Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmia, coronary artery disease, and other serious heart problems. Sudden death, stroke, and other serious heart problems taking CNS stimulants at recommended doses for ADHD. Further evaluate patients who develop exertional chest pain, unexplained syncope, or arrhythmias during DYANAVEL XR treatment.
• CNS stimulants cause increase in blood pressure (mean increase about 2 to 4 mm Hg) and heart rate (mean increase about 3 to 6 bpm). Monitor all patients for tachycardia and hypertension.
• CNS stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a preexisting psychiatric disorder. They may induce a mixed/manic episode in patients with bipolar disorder. Assess for presence of bipolar disorder prior to initiating treatment. At recommended doses, stimulants may cause psychotic or manic symptoms, e.g., hallucinations, delusional thinking, or mania, in patients without prior history of psychotic illness or mania. If such symptoms occur, consider discontinuing DYANAVEL XR (amphetamine).
Without reviewing her history—or noting that symptoms worsened with strong sunlight (or from reflected sunlight on snowy ski slopes)—the NP prescribed tramadol for pain and sent her on her way. Her family objected and drove her back to SoHo to see me. I was sorry to see Lilly in such distress, but I was happy to hear that she deferred starting a potentially habituating medication before exploring safer approaches or identifying the source of her symptoms.

Luckily, Lilly’s rural health center had ties with the regional medical school. They landed her an immediate immunology appointment at the State University of New York at Albany, not far from her family’s home. The good news was that she would be near her family, and she could continue to design for her new job remotely (but without accessing expensive metals that were available onsite only). Her father was thrilled to restart selling her creations from his truck, and she was relieved to return to a pace that was far simpler and slower than SoHo’s. She could rest up with relatives while awaiting more targeted treatment—and simultaneously brace for possibly bad diagnostic news.

This story did not have the happy ending that we hoped for, but the ending could have been worse. I shudder to think of what might have happened, or how this syndrome could have progressed, had someone summarily dismissed her symptoms as AEs of psychotropic medication, without additional assessment. Fortunately, psychiatrists are physicians first.

Dr Packer is an assistant clinical professor of psychiatry and behavioral sciences at Icahn School of Medicine at Mount Sinai in New York, NY.
Survey Finds 1 in 7 Physicians Uses Alcohol or Drugs on the Job to Cope With Stress

Richard Payurchin

One out of seven physicians admitted consuming alcohol or controlled substances while working to cope with occupational stresses, according to a new survey.

The findings were derived from the study “State of Mental Health: American Healthcare Workers Report,” which was commissioned by Edwards, Colorado-based AllPoints North (APN), a recovery and rehabilitation center that specializes in treating health care workers. The survey of 1,000 health care workers found that 21% of physicians—more than 1 in 5—consumed alcohol or controlled substances multiple times a day and 17% reported using at least once a day.

The results indicate high levels of substance abuse, an acute mental health crisis, and stigma within the healthcare industry,” APN founder and CEO Noah Nordheimer said in the report.

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DyanaVell® XR (amphetamine) extended-release tablets, for oral use, C1

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CNS stimulants, including DyanaVell XR, other amphetamine-containing products, and methylphenidate, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy.

INDICATIONS AND USAGE
DyanaVell XR is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). Sequelae syndrome symptoms of ADHD have been associated with weight loss and slowing of growth rate or mania in patients without prior history of psychotic illness or manic symptoms, e.g., hallucinations, delusional thinking, disorder, or depression). A preexisting psychotic disorder.

A patient on DyanaVell XR who has been treated with stimulants for a significant elevation in plasma corticosteroid levels.

DRUG ABUSE AND DEPENDENCE
Individuals who abuse amphetamines may use unapproved prescription records, educate patients and their families about abuse prior to prescribing. After prescribing, keep careful evaluation (e.g., rheumatology referral) may be appropriate for certain patients.

Serotonin Syndrome: Serotonin syndrome, a potentially life-threatening reaction, may occur when amphetamines are used in combination with other drugs that affect the serotonin neurotransmitter system (e.g., monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRs), triptans, tricyclic antidepressants, fentanyl, lamotrigine, and St. John’s Wort. The co-administration with cytochrome P450 2D6 (CYP2D6) inhibitors may also increase the risk with increased exposure to DyanaVell XR. In these situations, consider an alternative non-serotonergic drug or an alternative drug that does not inhibit CYP2D6. These drugs may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, tachycardia, blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., rigor, myoclonus, hyperreflexia, incoordination), and seizures. The use of the increased risk for serotonin syndrome. Initiate discontinuation with DyanaVell XR and any concomitant serotonergic agents immediately if symptoms of serotonin syndrome occur, and initiate supportive symptomatic treatment. If concomitant use of DyanaVell XR with other serotonergic drugs or CYP2D6 inhibitors is clinically warranted, initiate DyanaVell XR with lower doses, monitor patients for the emergence of serotonin syndrome during drug initiation or titration, and inform patients of the increased risk for serotonin syndrome during the use of DyanaVell XR with other drugs that affect the serotonin neurotransmitter system.

ADVERSE REACTIONS
Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. Clinical Trials Experience: DyanaVell XR is a controlled substance (C-1). With DyanaVell XR in Pediatric Patients with ADHD There is limited experience with DyanaVell XR in controlled trials. Based on this limited experience, the adverse reaction profile of DyanaVell XR appears similar to other amphetamine extended-release products. Adverse reactions occurring in ≥2% of subjects in the DyanaVell XR group (N=52) and greater than that in the placebo group (N=48) during the double blind phase of Phase 3 controlled studies in patients with ADHD aged 6 to 12 years were epigastric discomfort (DYANAVEL XR 5.50%, Placebo 6.0%), dyspepsia (3.8%, 6.0%) and upper abdominal pain (3.8%, 9%).

Postmarketing Experience: The following adverse reactions have been identified during post-approval use of other amphetamine products. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Alacritistic, anorexia, weight loss, irritability, euphoria, dysphoria, depression, tremor, aggression, anger,
system is too difficult to navigate (20%).

The study found a difference between men and women, with 58% of male health care workers reporting they were at their breaking point or were looking for a new job because of stress, burnout, and trauma, compared with 45% of women. Male health care workers reported struggling with substance misuse more than their female counterparts. Men were more likely to use their positions in health care to acquire controlled substances than women (21% versus 4%).

Men also were more likely to consume alcohol or controlled substances while at work (18% versus 4% of women) and were more likely to consume alcohol or controlled substances up to 12 hours before their shifts (44% versus 17% of women).

Pandemic Stress
Health care experts generally agreed workers were facing dangerous levels of burnout before COVID-19 spread, but the pandemic made things worse. As such, 40% of workers said they felt anxiety or dread about going to work, 49% said they were at their breaking point or looking for new work because of job stress and trauma, and 64% said the US Supreme Court decision overturning the Roe v Wade abortion rights case increased their stress levels or caused them to feel betrayed.

“The wellbeing and mental health of health care workers has been dramatically impacted by the pandemic, with many of them seeing more pain and death than ever before,” Nordheimer said in a news release. “This frequency and intensity of exposure is causing an unprecedented amount of trauma and stress, leading to high levels of burnout. The behavioral health care industry has been slow to innovate to meet the growing need for mental health care, oftentimes treating it as an accessory to health care. We must put mental health on par with physical health and make it a basic human right, an indicator of overall health, and an industry standard.”

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Drug: Having Clinically Important Drug Interactions With Amphetamines

MAO Inhibitors (MAOIs): MAOIs antidepressants slow amphetamine metabolism, resulting in a reduced inhibition of amphetamines effect on the release of norepinephrine and other monoamines from adrenergic nerve endings causing headaches and other signs of toxicity (e.g., fever, tremor, flushed face). Toxic neurological effects and malignant hyperpyrexia can occur sometimes with fatal results. Do not administer Dyanavel XR concomitantly or within 14 days following administration of MAO1. Serotonergic Drugs: The concomitant use of Dyanavel XR and serotonergic drugs increases the risk of serotonin syndrome. Initiate with lower doses and monitor for signs and symptoms of serotonin syndrome, particularly during Dyanavel XR initiation or dosage increase. If serotonin syndrome occurs, discontinue Dyanavel XR and the concomitant serotonergic drug. CYP2D6 Inhibitors: The concomitant use of Dyanavel XR and CYP2D6 inhibitors may increase the exposure of Dyanavel XR compared to the use of the drug alone and increase the risk of serotonin syndrome. Initiate with lower doses and monitor patients for signs and symptoms of serotonin syndrome particularly during Dyanavel XR initiation and after a dosage increase. If serotonin syndrome occurs, discontinue Dyanavel XR and the CYP2D6 Inhibitor. Alkalizing Agents (Trisorean and Gastrointestinal): Increase blood levels and potentiate the action of amphetamine. Co-administration of Dyanavel XR and trisorean or gastrointestinal agents should be avoided. Acidifying Agents (Trisorean and Gastrointestinal): Lower blood levels and efficacy of amphetamine. Increase dose based on clinical response. May enhance the activity of trycrocymy or sympathicomimetic agents causing flushing and sustained increases in the serum concentration of d-amphetamine in the brain; cardiovascular effects can be potentiated. Monitor frequently and adjust or discontinue the therapy based on clinical response.

Drug/Urinary Test Interactions Amphetamines can cause a significant elevation in plasma corticosteroid levels. This increase is greatest in the evening. Amphetamines may interfere with some urinary determinations.

USE IN SPECIFIC POPULATIONS

Pregnancy Pregnancy Registry: There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Dyanavel XR during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Psychostimulants at 1-866-961-2388 or visiting online at https://womenshealthfacts.org/clinical-and-research-programs/pregnancyregistry/或其他. Women should be encouraged to report all adverse events that occur to the use of amphetamines in pregnant women. These data are not yet available. Antidepressant associated major concurrent malformations or miscarriage. Adverse pregnancy outcomes include pre eclampsia and low birth weight, have been seen in infants born to mothers dependent on amphetamines. Clinical Considerations: Fetal/Neonatal adverse reactions: Amphetamines, such as Dyanavel XR, may cause vasoconstriction, including vasoconstriction of placental blood vessels, and may increase the risk for intrauterine growth restriction. In addition, amphetamines can stimulate uterine contractions increasing the risk of premature delivery. Premature delivery and low birth weight infants have been reported in amphetamine-dependent mothers. Monitor infants born to mothers taking amphetamines for symptoms of withdrawal, such as feeding difficulties, irritability, agitation, and excessive drowsiness. Lactation: Risk Summary: Based on limited case reports in published literature, amphetamine (d- or l-1) in present in human milk, at relative infant doses of 2% to 13.8% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging from 1.9 to 7.5. There are no reports of adverse effects on the breastfed infant and no effects on milk production. However, long term neurodevelopmental effects on infants from stimulant exposure are unknown. Because of the potential for serious adverse reactions in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with Dyanavel XR.
The Cross-Cultural Dimensions of Psychosis

Neil Krishan Aggarwal, MD, MBA, MA

Psychiatrists have been interested in the cross-cultural dimensions of psychosis since Emil Kraepelin (1856-1926) sailed to Java in 1904 and published his pivotal Vergleichende Psychiatrie (Comparative Psychiatry). Kraepelin provided the first known comparison of psychotic symptoms across populations: “The early stages of a depression were rarely seen, and violent excitement was also uncommon, but at the same time the very severe forms of dementia, so common in our own mental hospitals and found among the Europeans in Java as well, seem rarely to develop among the indigenous population.”

Today’s psychiatrists in North America and Europe do not need to go abroad to encounter individuals of different races and ethnicities. Affordable travel and developments in information technology have led to large-scale population migrations so that more physicians and patients identify as Black, Indigenous, and people of color (BIPOC).

Due to the increased likelihood of cross-cultural patient-clinician interactions, all medical students, psychiatry residents, fellows, faculty at academic medical institutions, and psychiatrists in independent practice in certain American states must develop skills in cultural competence to avoid perpetuating disparities in health outcomes for BIPOC individuals with serious mental illnesses. This raises a fundamental question of how to understand terms like culture and cultural competence.

"Culture refers to systems of knowledge, concepts, values, norms, and practices that are learned and transmitted across generations. Culture includes language, religion and spirituality, family structures, life-cycle stages, ceremonial rituals, customs, and ways of understanding health and illness, as well as moral, political, economic, and legal systems. Cultures are open, dynamic systems that undergo continuous change over time; in the contemporary world, most individuals and groups are exposed to multiple cultural contexts, which they use to fashion their own identities and make sense of experience."

The health services pathway can be divided into 4 discrete phases: help-seeking through first contact with a mental health clinician, receiving the diagnosis of a psychotic disorder, initiating treatment such as psychotherapy or pharmacotherapy, and adhering to treatment. Cultural differences among patients and clinicians affect each step.

HELP-SEEKING. Compared with those who are from majority ethno-racial populations in high-income North American and European countries, BIPOC individuals may make sense of their initial psychotic symptoms through shame and stigma, and are more likely to distrust psychiatrists based on experiences of racism, which delays their initial contact with mental health clinicians.

CASE 1: “Mrs Williams” is a Black American woman who contacts her son’s pediatrician about concerns related to behavioral changes. Her son’s teachers report that he stopped participating in classes. She thought his behaviors were part of normal adolescent development, but when he started to say that the US government wants to kill all Black individuals, she became concerned. Her pediatrician makes a referral to a child and adolescent psychiatrist who asks how long her son had been experiencing paranoid delusions. She says "about 9 months." He asks why she did not seek care sooner. She informs him that with so many instances in the news of Black males with mental illnesses experiencing violence from law enforcement officials, she did not want her son to be labeled. He evaluates her son, counsels her about first-episode psychosis, and gains her trust by guiding her through the special educational services process with the US Department of Education for her son to receive medical accommodations.
Clinicians collaborating with cultural and linguistic brokers and presenting cases in a multidisciplinary conference were able to re-diagnose 34 of 70 cases (49%) from a referral diagnosis of a psychotic disorder to a non-psychotic disorder.18

The Cultural Formulation Approach

Studies show that the cultural formulation approach can elicit the knowledge, concepts, values, norms, and practices that individuals with psychosis employ to make sense of their experiences. Researchers with McGill University’s Cultural Consultation Service have used an expanded version of the DSM-IV-TR Outline for Cultural Formulation to assess for cultural issues related to diagnosis, treatment planning, and treatment adherence. Clinicians collaborating with cultural and linguistic brokers and presenting cases in a multidisciplinary conference were able to re-diagnose 34 of 70 cases (49%) from a referral diagnosis of a psychotic disorder to a nonpsychotic disorder, and re-diagnose 12 of 253 (5%) cases from a referral diagnosis of a nonpsychotic disorder to a psychotic disorder.18

In changes discovered across diagnoses in all ethnic-racial groups, immigrants and refugees were misdiagnosed more with an initial psychotic disorder, showing that cultural information related to how individuals make sense of their experiences can affect diagnostic assessment and treatment selection.15

Many psychiatrists may not have access to a cultural consultation service or may find that cultural issues exist even with patients who share their ethnic, racial, and religious backgrounds. DSM-5 and DSM-5-TR include a series of semistructured interviews known collectively as the Cultural Formulation Interview (CFI), which the American Psychiatric Association has disseminated free of cost. The 16-question version for use with informants can be found at https://bit.ly/3yN-jvDr. A 17-item for use with informants can be found at https://bit.ly/3WLdRe.

Clinical studies show mixed results in individuals with psychosis. The interview can require more reflection on personal identity and treatment planning than can be tolerated by patients with florid hallucinations or paranoid delusions.16

However, stable outpatients with chronic illnesses felt that clinicians using the CFI validated their experiences and presented new avenues for recovery.17 Practicing clinicians may find the CFI useful when working with cultural minorities. It helps clinicians understand the cultural competence is a lifelong pursuit; tools like the CFI can help practitioners that first step.

Dr Aggarwal is an assistant professor of clinical psychiatry at Columbia University, and a research psychiatrist at New York State Psychiatric Institute in New York, New York.

References

Advances and Challenges in Adult ADHD

Heidi Anne Duer, MPH

Many advances have been made in the past 20 years in the field of adult attention-deficit/hyperactivity disorder (ADHD), explained Theresa Cerulli, MD, and Anthony L. Rostain, MD, MA, during a recent PsychView custom video program.

“The good news is that thanks to our efforts to educate both the public and health professionals about the fact that ADHD exists in adults, it has become more and more recognized by a growing number of people,” said Rostain, founding director of the Adult ADHD Treatment and Research Program and emeritus professor of psychiatry and pediatrics at Perelman School of Medicine at the University of Pennsylvania in Philadelphia. Nonetheless, Rostain and Cerulli, president and medical director of Cerulli & Associates in North Andover, Massachusetts, and lecturer and clinical supervisor at Harvard Medical School and Beth Israel Deaconess Medical Center in Boston, agreed there are still challenges in clinical practice, including biases and incomplete treatment response.

Recognizing and Addressing Biases and Barriers

Biases associated with the label of ADHD have caused barriers to care, according to Cerulli and Rostain. Rostain noted the mistrust among underserved communities that has resulted in undiagnosed cases. Unconscious bias may also sway clinicians’ judgments, mistaking ADHD for anxiety or depression.

Another possibility, Rostain said, is mistaking social impairment associated with adult ADHD as narcissistic personality disorder or other Cluster B kinds of disorders when, in fact, the underlying self-regulation leads to people having trouble acting in a way that we would say is either socially appropriate or not mature enough for their age.”

Cerulli added, “The other bias I see—especially with adult ADHD—is that a lot of people won’t come in because they are afraid that people are just going to think they’re seeking substances,” which results in delayed diagnoses.

“The stigma around stimulants is probably still one of the biggest hurdles we have to face,” Rostain said. “You hear the story again and again.” He said that patients have told him, “I know I had it as a young person, but my parents really weren’t willing to take me [to a doctor] because they didn’t want to have me start on a stimulant medication.”

Always looking for the positives, the pair agreed this presents an important opportunity for clinicians. “It is the job of psychiatrists and other mental health providers to say, ‘ADHD does not equal stimulants. ADHD is a condition; we need to understand it. It’s got a chronic and rather unremitting impact on functioning, and we need to approach it in a multiplicity of ways,’” Rostain said.

The Impact of Functional Impairment

Rostain and Cerulli agreed functional impairment plays a huge role in their patients’ lives. “I think that ADHD has become more and more impairing as our society evolves,” Rostain said. The impairment affects many aspects of patients’ lives—beyond work and school issues, Cerulli added.

“Most adults with ADHD have trouble with everything— from managing time, getting things done, and following directions,” Rostain explained. “There’s also the impulsivity side... managing emotions and being able to think before you speak or not just jump into a million different directions, but really being able to handle frustration, for example. And not getting into too many traffic accidents or getting speeding tickets.”

Managing personal and professional relationships can be troublesome too. Individuals with ADHD may be viewed as insensitive when they forget important appointments or interrupt people. “A lot of social rejection goes on,” Rostain noted. “It’s pretty obvious that as we look at data from national epidemiologic studies, the No. 1 comorbidity of adults with ADHD is social anxiety disorder. And that’s based a lot, I think, in having repeated experiences of social rejection or social failure.” “It’s really challenging for patients,” Cerulli concurred. “Divorce rate is twice as high when one spouse has ADHD, I really hope that people walk away understanding that ADHD is a problem with regulating attention, self-regulating behavior, control of one’s thoughts in terms of organizing, planning, time management—it affects everything.”

All that adds up, said Rostain, and can lead to low self-esteem. “There is a chronic sense of being inadequate, ineffective, and in some other way, not meeting others’ expectations. This can lead to some unfortunate coping mechanisms—overreliance on alcohol or substances, a tendency to overcommit and not be able to really deliver, and feeling constantly stressed out.”

Psychoeducation and Shared Decision-Making

The first step of treatment is psychoeducation, the pair noted. This includes the patient and their partner and/or close family members and should help define expectations. As patients understand what their brains do well—and what they do not do well—it is important to help teach skills that can support the patient, like making environmental adjustments and schedules. They noted communication skills might also improve relationships, especially when conflicts emerge. Rostain summarized this notion: “Pills don’t teach skills.”

Cerulli and Rostain also advocate for shared decision-making. Cerulli likes with patients about treatment and what’s important to the patient. She likes to give patients several options and sometimes shares the choices she might make for herself. “Shared decision-making empowers somebody who otherwise probably had low self-esteem... to pay attention to the details,” she said.

Rostain also uses shared decision-making to define goals, the methods for reaching those goals, and the time frame for achieving them. “There’s got to be a realistic sense that this is going to be a process and we’re embarking on it together. We’re going to try different things according to your priorities,” he explained. “The purpose of treatment is to help people function better. It’s not just to ‘reduce symptoms.’ It is improving the functioning in various domains of life. And that’s why it’s important to have it be a shared decision-making, real conversation.”

Cerulli agreed, noting DSM criteria and checklists only go so far, so it is crucial to find out what is important for each patient. “For some of them it’s, ‘I want to be able to have a conversation with my kids without getting mad—or with my partner.’ You know, for others, it’s, ‘I want to be able to get through my workday more effectively or more efficiently.’ For others it’s, ‘Hey, I want to be able to sit down and read a book and enjoy it.’ There are different priorities for people.”
Weighing and Making Treatment Choices

Although stimulants have generally been the first line of treatment, there are a number of choices to consider. Rostain and Cerulli said. Stimulants can be effective, but they can also be abused and have negative connotations associated with them. Plus, they do not work around the clock. Rostain said, adding that nonstimulants have the advantage of working 24/7 and without abuse potential, but their efficacy data are not as strong. Unlike stimulants, for which you can take a “medication holiday,” nonstimulants must be taken every day. For adults with ADHD, Rostain tends to look at the longer-acting stimulant preparations because adults tend to have longer days. “The big change in our way of looking at stimulants over the past decade or so has really been to look at the data and say, ‘Yeah, we get better adherence and fewer problems when we prescribe the long-acting medication preparation,’” he said.

So how does one choose between the amphetamine and methylphenidate options? “I always say talk with your patient about the differences in the profile. Find out if they have been on the medication. Many of our adult patients were treated as kids and have some remembrances of what did or did not work, or if other family members have been more or less successful on methylphenidate versus amphetamine,” Rostain said. However, if you think a patient may not want more than one medication trial, he said it might be better to start with an amphetamine because there is a slightly higher effect size compared with methylphenidate. He cautioned there is a greater risk of adverse effects (eg, appetite suppression, insomnia, a feeling of restlessness).

Cerulli agreed. “One question I ask, having learned secrets of my patients over the years,” she said, including that many patients have tried a sibling’s medication, “I will ask them with a wink and a nod if...they had experience with somebody else’s medication.”

In terms of abuse potential, Rostain share insights from colleagues in the substance abuse field. “Many have pointed out that the proper use of stimulants can actually reduce certain forms of substance use disorder,” he said. So instead of disregarding a medication type, it is important to ensure there is a comprehensive treatment plan in place and that the patient is monitored.

Next Steps to Consider When Improvement Stalls

Rostain recommends using a measurement (like the Adult ADHD Self-Report Scale) to measure goal progress. If using a stimulant and the highest safe dose has been tried and the patient remains symptomatic, Rostain tries an agent from the other safe dose has been tried and the patient remains symptomatic, Rostain tries an agent from the other field. “Many have pointed out that the proper use of stimulants can actually reduce certain forms of substance use disorder,” he said. So instead of disregarding a medication type, it is important to ensure there is a comprehensive treatment plan in place and that the patient is monitored.

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Mood Disorders

BIPOLAR UPDATE

Lithium: Cardiac Adverse Effects and When to Get an ECG

David N. Osser, MD

A recent consultation motivated an evaluation of the evidence on whether one should monitor electrocardiograms (ECGs) in patients taking lithium. Opinions vary and tend to be vague about when and how often to measure the ECG. Mogens Schou, MD, who was perhaps the world’s foremost expert on lithium and a passionate advocate for its use, observed that lithium occasionally changes the function or electrical activity of the heart, but the presence of heart disease rarely should prevent lithium treatment.1 If heart disease is present, however, he recommended a consultation with a cardiologist and serial ECGs might be considered. Much more recently, The Maudsley Prescribing Guidelines in Psychiatry from the United Kingdom recommended getting an ECG if there are risk factors for, or preexisting, cardiac disease—but offered no further details.2 In what appears to be the most thorough review of the subject, Mehta and Vannozzi proposed that, though data are limited, routine monitoring of ECGs seems unnecessary. However, if patients are maintained on or develop high lithium levels (eg, 1.2 mEq/L or higher), then the risks of arrhythmias, ST segment changes, and QRS prolongations become significant, and a baseline ECG and periodic repeats are worth doing.3 They also noted that lithium-induced ECG changes are more likely over the age of 60 years. This population has a high prevalence of ischemic heart disease, and the 2 most common lithium-induced changes (T wave inversions and sinus dysfunctions such as bradycardia) are also common manifestations of cardiac ischemia. Thus, it would be important to delineate the cause if such abnormalities were found. Therefore, Mehta and Vannozzi recommended a baseline ECG and follow-up at least every 6 to 12 months for anyone taking lithium for 10 years. Her ECG showed a wide range of abnormalities that, after excluding other factors, seemed mostly due to lithium as they were present even when her medical problems had resolved.4 There was atrial fibrillation acutely when her lithium level was 2.0 mEq/L (also found in some case reports in the Mehta and Vannozzi review and in another recent case report5), but this converted rapidly when the lithium level came down to normal. Six months later, with normal lithium levels, the patient still had ST segment elevation and inverted T waves. The report’s authors concluded that unpredictable genetic and comorbid illness factors could render a patient vulnerable to life-threatening arrhythmias if the right provocations come along, and the presence of abnormalities at therapeutic levels could predict who is vulnerable. Hence, they recommended that all patients receiving lithium should have an ECG and “regular” monitoring. They noted that these vulnerabilities might be more common in patients taking long-term lithium, hence the need for the continued monitoring.6 In summary, it seems that although there are no standardized, officially approved guidelines for serial ECG monitoring with lithium, we probably should be getting more baseline ECGs and repeating them more frequently in patients on long-term lithium and in those who develop cardiac risk factors. Consultation with our cardiology colleagues on any abnormal findings would be prudent.

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

References

Chemistry Lesson

Richard M. Berlin, MD

I was a Jewish boy from the Jersey burbs raised on corned beef and Milano cookies. She was a Mennonite farmgirl whose father shot deer for dinner.

And we were med students who’d fallen in love on our first date, pressed together three months later in her galley kitchen, butter and garlic sizzling in a black cast iron pan, steam rising from a pot of boiling water, torn Romaine waiting to be dressed in a buried wooden bowl, our truce broken only by her timer’s reminder to cook linguini and toss a Caesar salad. But I’d forgotten to stop for mayo!

Back then I believed Hellmann’s “Real” Mayonnaise was an element on the Periodic Table with an atomic weight nestled between Manganese and Molybdenum, a primordial substance the Hellmanns pumped from deep wells into millions of blue-lidded bottles they shipped across America. But before I made a hero’s gallant sprint to the market she forgave me with a smile, foraged eggs from the fridge, cracked them, separated the yolks, squeezed lemon juice, sprinkled salt, and whisked in oil until atoms fused for the miracle of mayonnaise, her steady green eyes and naked display of farmgirl skill the chemistry that bonded us for life.

Dr Berlin has been writing a poem about his experience of being a doctor every month for the past 24 years in the Psychiatric Times “Poetry of the Times” column. He is instructor in psychiatry, University of Massachusetts Medical School, Worcester, Massachusetts. His latest book is Freud on My Couch.
Bipolar depression (BD) can be difficult to treat due to several factors, and choosing the most appropriate treatment approaches should be based upon patient-specific factors (eg, comorbidities, preferences). Based on treatment response and these patient-specific issues, there are a variety of nonpharmacologic therapies and novel pharmacologic options that can be considered as part of the treatment plan.

Nonpharmacologic Interventions

Although many clinicians tend to focus on pharmacologic treatments for BD, nonpharmacologic interventions have been shown to be effective in bipolar depression, many of which contribute to an overall healthy lifestyle and can be recommended in addition to medications (Table 1). Additionally, some of these interventions pose only a low risk, and they may be preferable to the use of medications for select patients. Barriers associated with implementation include cost and accessibility. Clinicians should familiarize themselves with the following interventions and recommend them to patients whenever possible.

CHRONOTHERAPEUTIC TREATMENTS

The International Society for Bipolar Disorder recommends the use of chronotherapeutic treatments. Its guidelines recommend the use of bright light therapy and sleep deprivation/wake therapy for BD and dark therapy for mania. Several meta-analyses and systematic reviews found positive results for bright light therapy in BD. Although studies are relatively small, bright light has few to no adverse effects and should be considered for patients who have the resources to purchase a light box. In several meta-analyses, the brightness of the light box and length of time utilized varied, depending on the study. In most trials, the light provided ranged from 2500 to 10,000 lux, and the administration time ranged from 7.5 to 60 minutes delivered upon awakening in the morning. Patients interested in this approach, Veale provides an easy-to-follow method (Table 2). Although the directions are relatively simple, this protocol may be quite challenging for many patients due to the sleep restriction requirements.

The use of blue light-blocking sunglasses in the evening reduces depressive and manic symptoms. If patients have difficulty following the sleep deprivation and light therapy protocols, a middle ground might include wearing blue light–blocking glasses in

### Table 1. Nonpharmacologic Treatments for Bipolar Depression

<table>
<thead>
<tr>
<th>Nonpharmacologic Intervention</th>
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<tr>
<td>Chronotherapeutic treatments</td>
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<tr>
<td>Physical exercise</td>
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<tr>
<td>Smoking cessation</td>
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<tr>
<td>Anti-inflammatory diets (eg,</td>
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<tr>
<td>Mediterranean, MIND, ketogenic)</td>
</tr>
<tr>
<td>Supplements and nutriceuticals</td>
</tr>
<tr>
<td>Pain management</td>
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<td>Brain stimulation</td>
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(This is the second part of a 2-part article discussing novel treatments for bipolar depression. Part 1 appeared in the September issue and discussed the need for novel treatments for bipolar depression. –Ed)
the evening starting at 7 PM and doing bright light therapy every morning. Blue light–blocking sunglasses can be purchased for about $10, and light boxes with the appropriate specifications can be purchased for $100 to $200. There is some variability in light box specifications in the research; typically, a box measuring 12 x 17 inches is recommended. The brightness should be between 2500 and 10,000 lux, and patients should use the light box for about 30 minutes per day as soon as possible after waking up. The light box should be placed above eye level while in use, and sunglasses should not be worn.

The cost of the light box may be prohibitive for some patients. In those cases, clinicians should adapt suggested interventions to meet the patient’s needs. For example, patients may be able to sit outdoors in bright sunlight for 15 to 30 minutes in the morning.

PHYSICAL EXERCISE. Exercise has been shown to reduce inflammatory markers, and physical activity may be beneficial in BD. For example, Paolucci et al studied 61 university students engaged in various levels of exercise intensity. The investigators found moderate, continuous exercise produced the best results. Participants reported reductions in depression and anxiety, and they had lower levels of inflammatory markers. Of note, high-intensity interval training also improved depression, but it increased the participants’ perception of stress and increased the inflammatory markers TNF-α and interleukin-6. According to available literature related to the impact of exercise on numerous psychiatric conditions, exercise improves depressive symptoms, reduces stress, decreases inflammatory markers, and promotes the synthesis of monoamine neurotransmitters in patients with bipolar disorder. Although exercise alone may not lead to remission, it has clear benefits, and should be recommended at moderate levels. Easily accessible forms of exercise—such as walking—may be easiest for patients to implement. For patients who have mobility issues or who live in areas where walking is not possible, chair exercise or yoga might be good alternatives. Other patients may find it easier to set up an exercise schedule at a gym or with a personal trainer. Generally, an exercise program that the patient is most likely to maintain is the best choice.

SMOKING CESSATION. Data related to cigarette smoking and mental illness show a clear negative impact of smoking on the symptoms of BD. Indeed, smoking is a risk factor for the development of BD. Cigarette smoking is also well known to negatively affect inflammatory markers.

Although there is no evidence that smoking cessation will treat BD successfully, it makes sense to encourage all patients to stop smoking. Several effective pharmacologic and nonpharmacologic treatments are available to assist with this goal.

TABLE 2. Light Therapy and Sleep Restriction Guidelines

<table>
<thead>
<tr>
<th>Day</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>The patient stays awake all night. Napping is not allowed at any time during treatment.</td>
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<tr>
<td>Day 2</td>
<td>Bright light therapy with a light box or direct sunlight exposure occurs for 30 min between 6:45-9:00 AM. Blue light–blocking glasses are worn from 2:00 AM until bedtime at 5:00 AM. The patient rises at 1:00 AM.</td>
</tr>
<tr>
<td>Day 3</td>
<td>The patient remains awake all day. Bright light therapy is given at the same time as before. Blue light–blocking glasses are worn from 4:00 AM until bedtime at 7:00 AM. The patient rises at 3:00 AM.</td>
</tr>
<tr>
<td>Day 4</td>
<td>The patient remains awake all day. Bright light therapy is done at the same time. Blue light–blocking glasses are worn starting at 6:00 AM. Bedtime is at 9:00 PM.</td>
</tr>
<tr>
<td>Day 5</td>
<td>The patient remains awake all day. Blue light–blocking glasses are worn starting at 7 AM. Bedtime is at 11:00 PM. The patient rises at 7:00 AM.</td>
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Early evidence suggested that varenicline might worsen mood and increase the risk of suicidal ideation, but more recent analyses have not shown an increase in neuropsychiatric adverse effects with use of varenicline, bupropion, or nicotine replacement therapy. There are no concerning drug interactions with varenicline or bupropion and medications typically used to treat BD, but clinicians should be aware that cigarette smoking is a cytochrome P450 inducer. If patients quit smoking, the blood levels of some psychotropics can increase. Because the effect is related to smoking itself, the same interaction does not exist with nicotine replacement therapy.

DIETARY INTERVENTIONS. Healthy dietary patterns improve overall health and reduce symptoms of psychiatric illnesses. Specifically, the results of numerous studies have shown that following an anti-inflammatory diet can improve overall health and, potentially, psychiatric symptoms. Implementation of the Mediterranean diet and MIND (Mediterranean-Dietary Approaches to Stop Hypertension [DASH] Intervention for Neurodegenerative Delay) diets has anti-inflammatory properties. The Mediterranean diet is rich in antioxidants and flavonoids. It uses liberal amounts of whole grains, fruits, vegetables, nuts, olive oil, and omega-3 fatty acids, primarily through the consumption of fish. The MIND combines the benefits of the DASH, which was developed to prevent cardiovascular disease. It encourages reduced consumption of saturated fat, sodium, and sugar intake and promotes healthy proteins, whole grains, fruits, and vegetables. All of these diets have a variety of health benefits and anti-inflammatory properties that may aid in relieving depressive symptoms. Additionally, they may help combat the metabolic effects of numerous psychiatric medications.

When counseling patients about dietary change, clinicians may find it helpful to focus on a few specific items that patients can add to their current diets. Advising patients to overhaul their entire eating style may be overwhelming and ineffective. For example, patients may be able to focus on adding more vegetables, nuts, and seafood as a first step. In addition, small steps may be the best strategy for patients who consume great amounts of inflammatory foods such as sugar and starchy items. These individuals may find it less overwhelming if they focus on 1 change at a time (eg, switching from soda to water or flavored water) and then adopt other changes. Motivational interviewing approaches are useful when encouraging lifestyle change. Ideally, clinicians should check in with patients at every visit to monitor their progress in implementing lifestyle changes.

SUPPLEMENTS AND NUTRACEUTICALS. The results of several studies have noted that use of various dietary supplements may benefit patients diagnosed with BD and unipolar depression. Inflammatory state alterations reflective of microbiota alterations in the gastrointestinal (GI) system are present in many psychiatric conditions, including BD. Probiotics modulate stress hormones, increase brain-derived neurotrophic factor (BDNF) and serotonin levels, and reduce inflammation. The brain-gut axis involves pathways including the parasympathetic nervous system, the immune system, the gut neuroendocrine system, and neurotransmitters produced in the gut. For example, a large portion of endogenous serotonin is manufactured in the GI tract. Serotonin modulates the blood-brain barrier and vagal nerve activity.

Currently, evidence in humans on this topic is limited to observational studies. Probiotic supplementation may have a role in improving BD; current research, however, is limited by small trials and methodologic variability. Omega-3 fatty acids have anti-inflammatory properties, and may be effective in supporting treatment of BD. In a systematic review, Sarris et al found a positive effect for omega-3 fatty acids in depression. Additionally, several studies have shown positive effects for omega-3 fatty acids in patients diagnosed with BD. If using fish oil supplements, patients should ensure that the eicosapentaenoic acid (EPA) content is 1.5 times the amount of docosahexaenoic acid (DHA). In addition, patients should take between 1000 to 3000 mg per day. Most people are unlikely
TABLE 3. Potential and Emerging Novel Pharmacologic Agents

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism of action</th>
<th>Target dosing range</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dopaminergic agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amantadine</td>
<td>Dopamine agonist; NMDA receptor antagonist</td>
<td>100-200 mg per day</td>
<td>Anticholinergic, psychosis</td>
</tr>
<tr>
<td>Memantine</td>
<td>Dopamine agonist; NMDA receptor antagonist</td>
<td>10-20 mg per day</td>
<td>Anticholinergic, psychosis</td>
</tr>
<tr>
<td>Pramipexole</td>
<td>Dopamine agonist</td>
<td>Target dose, 1.5 mg per day</td>
<td>Nausea</td>
</tr>
<tr>
<td>Ropinirole</td>
<td>Dopamine agonist</td>
<td>2 mg per day</td>
<td>Nausea</td>
</tr>
<tr>
<td>Armodafinil</td>
<td>Dopamine agonist</td>
<td>150-250 mg per day</td>
<td>Appetite suppression, headache, mood switching, psychosis</td>
</tr>
<tr>
<td>Modafinil</td>
<td>Dopamine agonist</td>
<td>100-200 mg per day</td>
<td>Appetite suppression, headache, mood switching, psychosis</td>
</tr>
<tr>
<td>Amphetamine salts</td>
<td>Dopamine agonist</td>
<td>10-60 mg per day</td>
<td>Appetite suppression, mood switching, psychosis</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>Dopamine agonist</td>
<td>5-40 mg per day</td>
<td>Appetite suppression, hypotension, agitation, mood switching, psychosis</td>
</tr>
<tr>
<td><strong>Anti-inflammatory agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Celecoxib</td>
<td>COX-2 inhibitor</td>
<td>400 mg per day</td>
<td>Gastrointestinal ulcers, gastrointestinal bleeding</td>
</tr>
<tr>
<td>Minocycline</td>
<td>Tetracycline derivative</td>
<td>5-300 mg per day</td>
<td>Gastrointestinal upset, photosensitivity</td>
</tr>
<tr>
<td>N-Acetylcysteine</td>
<td>Modulator of cytokine production and glutathione</td>
<td>600 mg twice daily</td>
<td>Autoimmune disease</td>
</tr>
<tr>
<td>Omega-3 fatty acids</td>
<td>Anti-inflammatory agent</td>
<td>1000-3000 mg per day, EPA must be 1.5 times DHA</td>
<td>Fishy aftertaste, gastrointestinal upset</td>
</tr>
<tr>
<td><strong>Glutamatergic inhibitors/modulators and NMDA receptor antagonists</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Riluzole</td>
<td>Glutamate inhibitor; NMDA receptor antagonist</td>
<td>50 mg per day</td>
<td>Nausea, dizziness</td>
</tr>
<tr>
<td>Dextromethorphan</td>
<td>Glutamate modulator; NMDA receptor antagonist</td>
<td>30-60 mg per day</td>
<td>Dissociation, sedation</td>
</tr>
<tr>
<td>Ketamine and esketamine</td>
<td>NMDA receptor antagonist, glutamate modulator, synaptic plasticity enhancer</td>
<td>Varies based on administration method</td>
<td>Dissociation, confusion, psychosis, mood switching</td>
</tr>
<tr>
<td><strong>Antiglucocorticoid agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metyrapone, fluconazole, mifepristone</td>
<td>Glucocorticoid receptor inhibitor (specific MOA varies depending on drug)</td>
<td>Varies based on drug</td>
<td>Varies based on drug</td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>Thiazolidinedione; insulin resistance reducer</td>
<td>15-45 mg per day</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>Pindolol</td>
<td>β-blocker, 5HT₁ receptor antagonist</td>
<td>2.5-5 mg 3 times per day</td>
<td>Hypotension, bradycardia</td>
</tr>
<tr>
<td>T₃ and T₄</td>
<td>Thyroid hormone; possible modulator of monoamine levels and activity in the cortex</td>
<td>50-400 μg per day, although doses up to 300-600 μg per day have been studied</td>
<td>Tremor, headache, nausea, weight loss, bone density loss</td>
</tr>
</tbody>
</table>

to obtain this amount of EPA and DHA in their diet, unless they have a high intake of fish rich in omega-3 fatty acids.

Other supplements that have been studied in managing BD and unipolar depression include coenzyme Q10, inositol, and several vitamins and minerals. However, the evidence on these agents is very limited and has shown mixed findings. At this point, treatment recommendations cannot be made based on the research.

BRAIN STIMULATION. Transcranial magnetic stimulation (TMS) can be considered when standard treatments fail. Clinicians should be aware of a risk for psychomotor agitation in patients with BD who are treated with TMS. Currently, several FDA-approved devices are being used in patients with BD, and TMS is being used more commonly in this patient population. Deep brain stimulation (DBS) has been studied for BD, and has shown promising results. Several small studies showed that DBS provided significant improvement in depressive symptoms among patients with BD. Among the studies, there was no consistent brain area of focus for the DBS treatment; in TMS, on the other hand, the left dorsolateral prefrontal cortex was targeted. A risk for affective switching was seen in 1 patient among these trials, but adjustment of stimulation parameters mitigated the symptoms. DBS is not commonly used; however, it is surgically invasive and costly, and the device must be removed if treatment is not successful.

Electroconvulsive therapy (ECT) remains one of the most potent interventions for depressive disorders, including BD. The duration of the current episode is a significant predictor of therapeutic response, and some recommendations indicate that ECT should be considered earlier in the course of treatment. Unfortunately, many clinicians consider it a treatment of last resort. This stance may prolong the duration of a course of BD and reduce the likelihood of response.

Magnetic seizure therapy also is a promising treatment option. It delivers high-intensity magnetic field impulses through a coil to induce seizure activity in the brain. Currently, however, this treatment is not widely available.

**Novel Pharmacologic Interventions**

There is evidence supporting the use of various off-label pharmacologic treatments in BD (Table 3). Off-label medications typically are not included in published treatment guidelines, partially because research is less frequently conducted with older generic medications. Studies of off-label medications may show inconsistent findings due to smaller sample sizes and methodological variation. In addition, the majority of the systematic reviews and meta-analyses of these studies do not include information about the dosing ranges used, which limits their generalizability and clinical utility. When considering these novel medications, clinicians should consider them to be second-, third-, or fourth-line options, at best. Most importantly, clinicians should consider patient-specific factors that may influence treatment selection.

**Dopaminergic agents.** The use of dopaminergic agents (eg, dopamine antagonists, dopamine reuptake inhibitors) to treat depressive disorders is well established; indeed, dopamine antagonists...
are a mainstay of treatment according to published treatment guidelines. Other agents with varying mechanisms of action also have been studied. Amantadine and memantine are similar drugs that are believed to be dopamine agonists and NMDA-receptor antagonists. Typically, these drugs are used for Parkinson disease, dyskinesias, and neurocognitive impairment.

Although a small meta-analysis did not find a benefit for memantine over placebo to treat depression, another review found several studies that demonstrated positive effects. In addition, a case series demonstrated benefit with amantadine given for BD. Research on these agents remains limited, although they may be an option for patients with BD, particularly if affected patients have accompanying neurocognitive symptoms. In most studies, these drugs were used adjunctively with mood stabilizers.

Dopamine agonists and amphetamines have been studied for use in BD. Their efficacy has been demonstrated in RCTs, open label trials, and case report series. However, they run a risk of inducing mania and/or psychotic symptoms; therefore, clinicians should monitor patients closely for the emergence of such manifestations.

Modafinil and armodafinil typically are used to treat narcolepsy and sleep-wake cycle disorder. The results of 5 RCTs in a meta-analysis demonstrated that augmentation with modafinil/ armodafinil was associated with significantly greater rates of treatment response in patients with BD.

The dopamine agonists pramipexole and ropinirole are indicated to treat Parkinson disease and restless leg syndrome. A systematic review and meta-analysis involving 5 RCTs and 8 observational studies showed positive outcomes when pramipexole was used in patients with unipolar depression or BD. Two small studies found positive effects when ropinirole was used to treat BD or unipolar depression. Nausea is a common adverse effect associated with use of pramipexole; prophylactic use of an antinauseant may be advisable when treatment with the drug is initiated. On a positive note, pramipexole has not increased the risk of mood switching.

**ANTI-INFLAMMATORY AGENTS.** As discussed previously, chronic and acute inflammation may be related to depressive symptoms. There is preliminary evidence that biomarkers (eg, CRP, other inflammatory cytokines) may be elevated in people with bipolar disorder and other conditions affecting mood. A meta-analysis of 4 studies using infliximab, a TNF inhibitor, did not find positive effects when the drug was given to patients treatment-resistant unipolar depression. However, the use of other anti-inflammatory agents in the treatment of BD has some research support. For example, several studies have shown positive outcomes for celecoxib, a COX-2 inhibitor, when used adjunctively with standard treatments. Importantly, a concurrent proton-pump inhibitor to protect the GI system should be prescribed when using celecoxib.

Minocycline is a tetracycline derivative antibiotic that also has anti-inflammatory properties. A small RCT showed positive effects for its use in patients with unipolar depression. A systematic review found positive effects in treating schizophrenia but not BD or unipolar depression; 16 RCTs were included, although only 1 focused on BD, and 3 focused on unipolar depression. In addition, there was a wide dosing range among studies (50-300 mg) and some methodological variation, making generalizations difficult.

N-acetylcysteine (NAC) is another anti-inflammatory agent that has been studied to treat BD. This drug primarily has been used to treat acute liver injury, but it is also available as an over-the-counter supplement. It has anti-inflammatory effects believed to be related to modulation of cytokine production and glutathione, an antioxidant that modulates NMDA receptors that may be related to the therapeutic effect of NAC. Several reviews included trials demonstrating the efficacy of NAC in treating BD.

Statins drugs used to treat hypercholesterolemia exert anti-inflammatory effects, as well. Research on using these agents to treat psychiatric disorders is very limited; however, there are some potentially promising findings involving schizophrenia, unipolar depression, and dementia.

**GLUTAMATERGIC INHIBITORS AND NMDA RECEPTOR ANTAGONISTS.** Riluzole is believed to function as a glutamate inhibitor and an NMDA receptor antagonist. It is indicated as a treatment for amyotrophic lateral sclerosis. Lamotrigine, also a glutamate inhibitor, is more commonly used in psychiatry. A literature review provided preliminary evidence supporting riluzole use in patients with depression or several other psychiatric disorders. Similarly, a small, open-label study of glutamatergic neurotransmission and depressive symptoms in BD showed an improvement in depressive symptoms with the use of riluzole.

Dextromethorphan is another glutamate modulator and NMDA receptor antagonist. There is evidence supporting its adjunctive use with standard medication treatments in mood disorders. Dextromethorphan has been studied as a combination therapy with quinidine and as a mono-therapy.

**ANTIGLUCOCORTICOID AGENTS.** Antiglucocorticoid drugs that have been investigated for use in mood disorders include metyrapone, ketoconazole, and mifepristone. In a meta-analysis, individuals with depressive symptoms associated with unipolar depression and higher cortisol levels at baseline responded to metyrapone and ketoconazole. Also discussed in this meta-analysis was the use of mifepristone for patients with psychotic depression or bipolar disorder. Evidence on mifepristone in BD is limited, but use of this drug in affected patients has produced promising results—baseline cortisol levels were similar among responders and nonresponders. Again, these small studies had methodological variability.

**MISCELLANEOUS AGENTS.** Other miscellaneous agents that have been studied for BD include pioglitazone (an anti-diabetic agent), pindolol (a β-blocker that also blocks 5-hydroxytryptamine 1A receptors and possibly exerts antidepressant effects through that mechanism), and liothyrone sodium (T₃) and levothyroxine sodium (T₄) hormone supplementation. The results for these agents have been mixed. For example, although an RCT found positive effects of pioglitazone, another failed to show benefit. Pindolol has been studied as an adjunct to dark therapy and has significantly improved the antidepressant effects of sleep deprivation. In addition, there is evidence to support the use of T₃ and T₄ as an augmentation strategy. The use of thyroid hormone augmentation in unipolar depression is well established; however, research in BD is more limited. In practice, T₃ is often preferred due to cost and availability, but there is evidence that T₄ may be more effective.

**Concluding Thoughts**

Although there are a number of FDA-approved medications and published treatment guidelines related to the treatment of BD, the established medications are often ineffective or intolerable...
due to adverse effects in many cases. Fortunately, there are a variety of emerging nonpharmacologic and pharmacologic options to treat BD when standard treatments have failed. The majority of nonpharmacologic treatments have minimal to no adverse effects and they contribute to an overall healthy lifestyle. Physical exercise, light box therapy, or an anti-inflammatory diet can be excellent therapeutic options for some patients. Medications with mechanisms of action other than those of standard pharmacologic treatments may be sensible third- or fourth-line therapeutic options. Psychiatric clinicians would be well-served by familiarizing themselves with novel treatment choices for BD and applying an individualized approach to enhance patient outcomes.

NP Hardy is a psychiatric mental health nurse practitioner and clinical assistant professor at the Virginia Commonwealth University School of Nursing. Mr. McCarthy is a psychiatric mental health nurse practitioner at the Mood Treatment Center in Winston-Salem, North Carolina.

References
3 Things You Should Know About New Updates in Managing Psychiatric Disorders

Release Date: November 1, 2022
Expiration Date: November 1, 2023

Learning Objectives
Upon successful completion of this activity, you should be better prepared to:
• Apply effective strategies for screening and diagnosing patients with psychiatric disorders
• Incorporate recent guidelines and evidence to the treatment of patients with psychiatric disorders

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Screening for developmental trauma can help determine treatment needs.

Adverse childhood experiences (ACEs), also referred to as developmental traumas, are potentially traumatic events that take place during childhood and adolescence and may include abuse, neglect, exposure to interpersonal violence and parental loss. In many cases, children are exposed to multiple ACEs. The event(s) of overwhelming stress may be greater than the child’s adaptive capacity, and they can have irreversible neurological effects during crucial developmental periods, resulting in changes in the child’s ability to regulate stress throughout their entire life.

Multiple ACEs increase health risks in adulthood. Exposure to chronic, cumulative stress affects development of the nervous, endocrine and immune systems throughout life. The presence of ACEs is also associated with a variety of physical and mental health problems during and after childhood, including psychiatric disorders such as anxiety, depression, and post-traumatic stress disorder. It is critical for healthcare providers to screen for ACEs and address them with support and intervention.

To learn more about the diagnosis and management of psychiatric disorders, go to www.gotoper.com/aptcme22-r

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3. Answer the evaluation questions.
4. Request credit using the drop-down menu.
You may immediately download your certificate.

The treatment of psychiatric diseases is evolving with advances in imaging and understanding brain circuitry, which bring new strategies for early diagnosis and intervention of complex psychiatric conditions. Updated therapeutic approaches are improving the treatment of many mental health disorders. It is important that psychiatrists and other members of the multidisciplinary care team understand the latest clinical advances and how to best apply that knowledge into practice. At the 2022 Annual Psychiatric Times™ World CME Conference™, expert faculty reviewed the latest developments in the field. Here are 3 things you should know about new updates in managing psychiatric disorders.
Repetitive transcranial magnetic stimulation and electroconvulsive therapy may be considered for difficult-to-treat psychiatric disorders.

In repetitive transcranial magnetic stimulation (rTMS), a magnetic coil is used to provide a repeated magnetic pulse of the same intensity to a distinct area of the brain, inducing an electric current strong enough to directly activate neurons. Decreased activity of the dorsolateral prefrontal cortex is commonly linked to the pathophysiology of depression, and this area of the brain is targeted by rTMS when used for treatment-resistant depression. Patients undergo 5 sessions of rTMS per week for 4–6 weeks.

In clinical trials, rTMS significantly improved symptoms of depression compared with sham treatment, and adverse events were generally mild. Overall, rTMS is considered safe, noninvasive, and well tolerated, with the most common adverse effect being transient headache. However, rTMS is time consuming and not always covered by insurance; it also has rare risks of seizure, local pain and scalp burns.

In addition to treatment-resistant depression, rTMS is being investigated for many other applications. The FDA has approved the use of rTMS for obsessive-compulsive disorder and smoking cessation.

Electroconvulsive therapy (ECT), which has been used for severe treatment-resistant depression for many years, involves the use of an electrical stimulation to generate a seizure in the brain while the patient is under anesthesia. It has been associated with rapid response and remission, but the optimal placement of electrodes is still being determined. Because retrograde memory loss is a serious safety concern, the decision to use ECT in patients who have failed multiple other options should be individualized.

The three-hit model for vulnerability and resilience is a useful framework for perceiving the impact of developmental trauma on the patient and its consequences for clinical management. According to this model, an individual’s genetic background (hit-one) combined with early-life stress (hit-two) causes an evolving phenotype characterized by altered stress regulation. When the patient is exposed to challenges later in life (hit-three), the vulnerability risk depends on the type of challenge presented and other individual factors, such as coping strategies, lifestyle and existence of support.

Developmental trauma is commonly linked to posttraumatic stress disorder (PTSD). In patients who develop PTSD, trauma-focused psychotherapy is an essential first-line treatment. If pharmacotherapy is used, sertraline and paroxetine are FDA-approved for PTSD.

Scores patients from 0–10, based on how many of the 10 categories of ACEs they have experienced

Expands on the ACES questionnaire for adults and inquires about how childhood trauma currently affects the patient

A measure of exposure to 14 distressful events, levels of exposure and duration of distress

The FDA has approved the use of rTMS for obsessive-compulsive disorder and smoking cessation.

CONTINUING MEDICAL EDUCATION

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For a full list of references go to www.gotoper.com/3tsk22mpd-art
Identifying “State of the Art Treatment” for MDD

Is there one state-of-the-art treatment for depression? “No, that was the dilemma I faced in trying to prepare for this talk,” Sidney Zisook, MD, shared with attendees of the 2022 Annual Psychiatric Times™ World CME Conference held in August in San Diego, California.

“There is no state-of-the-art treatment because major depressive disorder [MDD] is such a broad, diverse, heterogeneous group of symptoms,” explained Zisook, who is distinguished professor at the University of California, San Diego, and a previous recipient of the Psychiatric Times™ Educator of the Year Award. “In fact, there are 227 possible combinations of symptoms that will allow a person to meet the DSM criteria for major depressive disorder. And, in addition to the symptomatic heterogeneity, there are a host of other issues that affect this: severity—mild symptoms versus very severe problems; clinical features—are there anxious features, atypical features, or melancholic features? All of these may lead us to different approaches that we may take with that patient.”

Because of this, there are a number of issues and features that should be assessed for each patient. Zisook discussed a recent review that revealed 14 key areas: symptom profile, clinical subtypes, severity, neurocognition, functioning and quality of life, clinical staging, personality traits, antecedent and concomitant psychiatric conditions, physical comorbidities, family history, early and recent environmental exposures, protective factors, resilience, and dysfunctional cognitive schema.1

Thus, the best care practice—which is really what makes for state-of-the-art treatment for MDD—relies on a thorough history, Zisook said. “A really thorough history begins with lab studies, physical exam, etc.” he said. “But the initial assessment is not enough. We want to repeat the workup for patients who aren’t doing well over time.”

“I can’t tell you how many times in my career, when I redid my initial assessment 6 months down the line and somebody wasn’t having a good response, how different that history was and how I now—for the first time—learned about their drinking history and the cocktails they had every night. Or their early life trauma that was very much affecting their day-to-day life as an adult, etc. So not only do you do good assessment to begin with, repeat it intermittently as you have a better relationship with the patient to get a better, fuller picture of who they are,” Zisook said.

This includes checking for co-occurring conditions and ensuring treatment for those conditions, too, said he explained.

Similarly, he said it is important to use measurement-based care to inform decisions. “Several studies’ have found that if you measure symptoms, if you measure side effects, even with a global side effect measure along the way, share those with the patients, and develop a diary of symptoms and tolerance, you’ll actually end up with better results,” Zisook reported.

Then, clinicians should dip into the wide variety of choices from what he called the “2022 Antidepressant Tool Kit.” In terms of medication choices, Zisook told attendees all FDA-approved antidepressants (ie, tricyclics, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, serotonin modulators, and atypical antidepressants, and novel nonmonooamines) are equally effective with some differing adverse effects.

When discussing medication treatment personalization, the topic of pharmacogenomic testing often comes up, said Zisook. “There was a lot of excitement about pharmacogenetic testing a few years ago. A lot of that excitement has died down because it hasn’t really proven to have a dramatic impact on our ability to personalize medications,” he told attendees.

However, testing can provide information on the genes involved in the metabolism of antidepressants (eg, CYP2D6, 2C19, 1A2, 2C9, 342, and 2B6), how the drug may be metabolized in patients, and whether the medications should be used as usual, with caution, or with extra caution and increased monitoring. “If they [patients] are a very poor metabolizer, they may end up with a very high dose of the medication that you’re providing in their system, and they may be more prone to significant side effects adversity and tolerance, etc. You may need to go slower or lower or avoid certain medications,” he advised attendees.

Brain stimulation options (ie, bright light therapy, electroconvulsive therapy, transcranial magnetic stimulation, and vagus nerve stimulation) are also effective strategies in the tool kit, he noted.

Furthermore, Zisook reminded conference attendees not to overlook the potential of psychotherapy as part of the treatment strategy.

“A recent survey showed only about 20% of psychiatrists do psychotherapy in their offices, but...
even though we all know that psychotherapy plus meds is better than meds alone."

Lifestyle aids, like exercise, are also important and should be considered as part of the treatment plan, he noted. "I tell all my patients, 'When you're feeling more energetic, when you're up to it, start exercising. Get out of the house, take advantage the sunlight.' They may not be able to do it initially. But I plant the seed early on and go back to it."

The therapeutic alliance is key to success, Zisook said, and sometimes may be overlooked. He shared results from a National Institute of Mental Health study that found psychiatrists can "augment the effects" of both the medications as well as placebo. "Those patients who had the best results even with placebo were the ones that maximized the nontherapeutic, nonspecific factors that are common to psychotherapy that's effective, like developing a therapeutic alliance; getting a trustful, empathetic, and collaborative relationship with a patient," he said.

"Take advantage of those factors—and yourself," Zisook advised. "This may mean spending more than 20 minutes with a patient. It may mean seeing their family. It may mean talking about their life independent of their depressive symptoms. But that relationship is critical in helping many of our patients get better."

Zisook concluded by reminding conference attendees of their network of support and the importance of engaging colleagues as needed.

"Never worry alone," he said. "It's always so nice when you're treating people with depression—especially difficult to treat depression—to have a colleague, other people that you can work with, you can consult with, to talk about patients. And I've always found that a critical part of my overall practice."

References

Covering the Basics:
Terminology
Valeria Roldán; Z Paige Lerario, MD, NYS CRPA/CPS-provisional

Being well versed in correct terminology is fundamental to building affirming clinical environments and psychosocial rapport with patients. Physicians are not expected to get everything right, but to take responsibility for their education and apologize in the event a mistake is made.

First, a key distinction to make is between sex and gender. Sex is assigned at birth by a medical professional most often based on biological criteria, such as external genitalia. Gender refers to a person's internal sense of self, which can be expressed through a diverse range of social, cultural, physical, and behavioral cues, such as clothing, pronouns, and physical embodiment. The Figure defines these terms and their key differences.

Second, neither sex nor gender are binary, as evidenced by the existence of intersex and TGD individuals. And neither sex nor gender are categorical. Someone's gender identity can change through their life, and someone's sex can, too (eg, a person can change their gender expression, sex hormone levels, and the appearance of their genitalia).

Third, another common misconception is that gender identity is the same as sexual orientation, which refers to the gender(s) of the individuals to whom a person is attracted. This includes asexual people, who do not experience sexual attraction. Many TGD individuals identify as "straight," or heterosexual. Self-disclosing a TGD identity does not necessarily mean that the person is "gay/lesbian," or homosexual.

Last, terminology changes depending on geography and demography. For example, in Latin America, terms such as transsexual and travesti are used as synonyms for transgender. However, these may be considered derogatory in the United States and Europe due to their medical implications.

Beyond Sex
An introduction to terminology on gender, sex and sexual orientation.

GENDER IDENTITY
A person’s internal sense of their gender.

CISGENDER
Someone whose gender aligns with their sex assigned at birth.

TRANSGENDER
Someone whose gender identity differs from their sex assigned at birth.

NON BINARY
Someone whose gender identity isn’t within the binary man/male or woman/female. They may identify as both (bigender), as neither (agender) or a gender identity that changes in expression or intensity (genderfluid).

GENDERQUEER/GENDER NON CONFORMING
People who display non-normative gender roles, expressions and identities as defined by cultural expectations for their sex assigned at birth.

INTERSEX
Those whose sex-defining characteristics or reproductive anatomy don’t fit the binary male/female. Also know as “disorders of sex development”

SEXUAL ORIENTATION
Genders of the individuals towards whom someone is attracted. The reference point for someone’s sexual orientation is gender not sex assigned at birth.

GAY/LESBIAN
Someone who is attracted to the same gender.

STRAIGHT
Someone who is attracted to a different gender. Ex: A trans woman who is attracted only to men.

BISEXUAL
Someone who is attracted to more than one gender. Recently, it is preferred to use the term pansexual as it doesn’t imply a gender binary and it includes trans and nonbinary identities.

QUEER
A reclaimed slur for sexual orientation or gender identity outside the norm.

SEX (ASSIGNED AT BIRTH)
Construct that can induce characteristics of external genitalia, gonads, hormone levels and chromosomes, among other variables.

With the continued growth of our Department of Psychiatry and our New General Psychiatry Residency Programs at Ocean Medical Center and Jersey Shore University Medical Center our vision for Behavioral Health is Bright.

Hackensack Meridian Health is a leading not-for-profit health care network in New Jersey offering a complete range of medical services, innovative research, and life-enhancing care aiming to serve as a national model for changing and simplifying health care delivery through partnerships with innovative companies and focusing on quality and safety.

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

The School of Medicine will be the anchor in the development of a comprehensive health sciences campus that will also include research facilities and biotechnology endeavors – all in service of educating tomorrow’s doctors, discovering novel therapies, and facilitating compassionate and effective healthcare that will meet the ever-changing needs of tomorrow’s patients.

The School of Medicine will be the cornerstone of a dynamic venue for the exchange of ideas, the development of healthcare and research thought leaders and practitioners, and the discovery of novel therapies to meet the medical challenges of the future.

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

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

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

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

**Consultation Liaison:** Hackensack University Medical Center (Hackensack, NJ)

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

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

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

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

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

**Outpatient:** Jersey Shore University Medical Center (Neptune, NJ) Ocean University Medical Center (Brick, NJ) and Southern Ocean Medical Center - (Manahawkin, NJ)

**TelePsychiatry:** Fully Remote, full-time opportunities (Work from anywhere!)

If you’re interested in this exciting opportunity, email your CV to careers@dsh.ca.gov today!

**Salary and Benefits**

- $323,004 - $383,916/year
- Flexible workweek options may be available
- Substantial continuing medical education
- Defined-benefit pension (subject to Safety Retirement)
- Medical, dental and vision benefits
- Private practice permitted
- Retiree healthcare
- Patient-centric, treatment first environment
- Relocation assistance may be available

If you’re interested in this exciting opportunity, email your CV to careers@dsh.ca.gov today!

**Psychiatrists:**

We’re recruiting Medical Directors

We invite you to join our team! The California Department of State Hospitals (DSH) is the largest forensic mental health hospital system in the nation. We’re looking for qualified psychiatrists to work as Medical Directors at our locations in California.

As a Medical Director at a DSH hospital, you will serve as the primary physician leader of the hospital. You’ll have the opportunity to oversee clinical practice, diagnostic and evaluative activities, treatment programs, and care of patients at the facility you’re working at.

DSH offers an outstanding quality of practice; we maintain a number of academic partnerships and promote a team-oriented, collegial working environment. We also offer all our psychiatrists a competitive salary, a world-class benefits package, and excellent work-life balance.

If you’re interested in this exciting opportunity, email your CV to careers@dsh.ca.gov today!
California

Outpatient Psychiatry Opportunity
San Joaquin County Behavioral Health Services is seeking to fill Outpatient Adult [General], and Sub-Specialty Psychiatry (Child Psychiatry, Geriatric, Forensic, Addiction and Psychosomatic Medicine) positions in a multidisciplinary, recovery-oriented clinical setting. Services are provided either on-site or using a hybrid model of on-site and tele-psychiatry practice. The positions offer a very competitive salary with a guaranteed base, plus incentive opportunities, board certified Psychiatrists have the potential to easily earn over $300K+ a year; comprehensive health insurance; up to three retirement and pension programs; 35 days of vacation and CME time that increase with tenure. Signing and moving bonuses are also available.

Interested J-1 and H-1B candidates are welcome to apply. Fax your CV to 209-468-2399 or email to BHSadministration@sjcbhs.org. EOE

BHSadministration@sjcbhs.org. EOE/AA Employer.

North Carolina

SEEKING FT/PT CHILD & ADOLESCENT/ADULT PSYCHIATRIST (BE/BC)

San Juan Health Partners in Farmington, New Mexico is recruiting one General Psychiatrist for primary outpatient coverage plus call and one General Psychiatrist for primary outpatient coverage plus call. Join a caring, community hospital in the heart of the Four Corners.

Find What You’re Looking For Now

Log on to PsychiatricTimes.com/classifieds to view our extensive list of jobs

You can look forward to:
- Compensation range based on years of experience
- Less than two years of experience $277,000
- Two or more years of experience $310,000
- 1:3 call
- Productivity/quality bonus potential
- Lucrative benefit package, including retirement
- Student loan repayment and residency stipend
- Competitive sign on bonus and relocation package
- Quality work/life balance

San Juan Regional Medical Center is a non-profit and community governed facility. Farmington offers a temperate four-season climate near the Rocky Mountains with world-class snow skiing, fly fishing, golf, hiking and water sports. Easy access to world renowned Santa Fe Opera, cultural sites, National Parks and monuments. Farmington’s strong sense of community and vibrant Southwest culture make it a great place to pursue a work-life balance.

Contact Terri Smith | 888.282.6591 or 505.609.6011 (phone) | tsmith@sjrmc.net
(email) | sanjuanregional.com or sjrmdocs.com
Maryland

PGS
PsychoGeriatric Services
F/T OR P/T
To work in Nursing home setting. Very flexible hours and good support team. Administrative plus clinical work. Great income potential and opportunity to become a partner. Interested candidates contact nramesh@pgs-nhcare.com

Missouri

Compass Health Network, is a large non-profit health system delivering Behavioral Health services in multiple settings, both inpatient and outpatient in forty-six Missouri counties. We have immediate openings for full and part-time Psychiatrists in multiple locations in Missouri. Candidates must have MD or DO degree, be ABPN board-certified or eligible in Psychiatry and possess or obtain a Missouri license. We offer a competitive compensation and benefit plan.

Apply online at www.compasshealthnetwork.org or send your CV to cgripp@compasshn.org. Candidates with J-1 or H1-b visa status are welcome to apply. EOE

Pennsylvania

PSYCHIATRISTS
AmeriCare Services is pleased to announce excellent full time opportunities with our group in several locations throughout, Pennsylvania. The positions are inpatient, Monday thru Friday with no on-call, weekend, evenings or holidays. The compensation is $220.00 per hour.

For confidential consideration call 610-695-8521 or email: KGallagher@AmCareServices.com
ADVERSE REACTIONS

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

- Hypersensitivity
- Somnolence
- QT Prolongation
- Parkinsonism

Clinical Trials Experience

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

Variable and Fixed Dose Placebo-Controlled Trial Experience

The safety of INGREZZA was evaluated in 3 placebo-controlled studies, each 6 weeks in duration (fixed dose, dose escalation, dose reduction), including 445 patients. Patients were 26 to 84 years of age with moderate to severe tardive dyskinesia and had concurrent diagnoses of mood disorder (27%) or schizophrenia/bipolar disorder (4%). With respect to ethnicity, 28% were Hispanic or Latino. All subjects continued previous treatment including 197 patients taking other agents for tardive dyskinesia. In the 3 placebo-controlled clinical studies in patients with tardive dyskinesia, the incidence of parkinson-like adverse events was 3% of patients treated with INGREZZA and <1% of placebo-treated patients. Postmarketing safety reports have described parkinson-like symptoms, some of which were severe and required hospitalization. In most cases, severe parkinsonism occurred within the first 2 weeks after starting or increasing the dose of INGREZZA. Associated symptoms have included falls, gait disturbances, tremor, draping, and hypokinesia. In cases in which follow-up clinical information was available, parkinson-like symptoms were reported to resolve following discontinuation of INGREZZA therapy. Reduce the dose or discontinuation INGREZZA treatment in patients who develop clinically significant parkinson-like signs or symptoms.

ADVERSE REACTIONS Leading to Discontinuation of Treatment

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

Common Adverse Reactions

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

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>INGREZZA (n=262) (%)</th>
<th>Placebo (n=183) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>10.9%</td>
<td>4.2%</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Akathisia (akathisia, restlessness)</td>
<td>5.4%</td>
<td>4.9%</td>
</tr>
<tr>
<td>Balance disorders (fall, gait disturbance, dizziness, balance disorder)</td>
<td>4.1%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Headache</td>
<td>3.4%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Akathisia (akathisia, restlessness)</td>
<td>2.7%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>2.6%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Nausea</td>
<td>2.3%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Pulmonary Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2.3%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

Other Adverse Reactions Observed During the Premarketing Evaluation of INGREZZA

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

Endocrine Disorders: blood glucose increased

General Disorders: weight increased

Infectious Disorders: respiratory infections

Neuropsychiatric Disorders: dizziness, dyskinesia, extrapyramidal symptoms (non-akathisia)

Psychiatric Disorders: anxiety, insomnia

Drug Interactions

Drugs Having Clinically Important Interactions with INGREZZA

Monoamine Oxidase Inhibitors (MAOIs)

Clinical Implication:

Concurrent use of INGREZZA with MAOIs may increase the concentration of monoamine neurotransmitters in synapses, potentially leading to increased risk of adverse reactions such as serotonin syndrome, or attenuated treatment effect of INGREZZA.

Prevention or Management:

Avoid concomitant use of INGREZZA with MAOIs.

Examples:

isocarboxazid, phenelzine, selegiline

Strong CYP3A4 Inhibitors

Clinical Implication:

Concomitant use of INGREZZA with strong CYP3A4 inhibitors increased the exposure (Cmax and AUC) to valbenazine and its active metabolite compared with the use of INGREZZA alone. Increased exposure of valbenazine and its active metabolite may increase the risk of exposure-related adverse reactions.

Prevention or Management:

Reduce INGREZZA dose when INGREZZA is coadministered with a strong CYP3A4 inhibitor.

Examples:

itraconazole, ketoconazole, clarithromycin

Strong CYP2D6 Inhibitors

Clinical Implication:

Concomitant use of INGREZZA with strong CYP2D6 inhibitors increased the exposure (Cmax and AUC) to valbenazine’s active metabolite compared with the use of INGREZZA alone. Increased exposure of valbenazine and its active metabolite may increase the risk of exposure-related adverse reactions.

Prevention or Management:

Reduce INGREZZA dose when INGREZZA is coadministered with a strong CYP2D6 inhibitor.

Examples:

paroxetine, fluoxetine, quinidine

Strong CYP3A4 Inducers

Clinical Implication:

Concomitant use of INGREZZA with a strong CYP3A4 inducer decreased the exposure (Cmax and AUC) to valbenazine’s active metabolite compared to the use of INGREZZA alone. Reduced exposure of valbenazine and its active metabolite may reduce efficacy.

Prevention or Management:

Concomitant use of strong CYP3A4 inducers with INGREZZA is not recommended.

Examples:

rifampin, carbamazepine, phenytoin, St. John’s wort

Digoxin

Clinical Implication:

Concomitant use of INGREZZA with digoxin increased digoxin levels because of inhibition of intestinal P-glycoprotein (P-gp).

Prevention or Management:

Digoxin concentrations should be monitored when coadministering INGREZZA with digoxin. Increased digoxin exposure may increase the risk of exposure-related adverse reactions. Dosage adjustment of digoxin may be necessary.

Distributed by:

Neurocrine Biosciences, Inc.
San Diego, CA 92130

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**INDICATION & USAGE**

**INGREZZA** is indicated for the treatment of adults with tardive dyskinesia (TD).

**CONTRAINDICATIONS**

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

**WARNINGS & PRECAUTIONS (continued)**

**Parkinsonism**

INGREZZA may cause parkinsonism in patients with tardive dyskinesia. Parkinsonism has also been observed with other VMAT2 inhibitors. Reduce the dose or discontinue INGREZZA treatment in patients who develop clinically significant parkinson-like signs or symptoms.

**ADVERSE REACTIONS**

The most common adverse reaction (≥5% and twice the rate of placebo) is somnolence. Other adverse reactions (≥2% and >Placebo) include: anticholinergic effects, balance disorders/falls, headache, akathisia, vomiting, nausea, and arthralgia. You are encouraged to report negative side effects of prescription drugs to the FDA. Visit MedWatch at [www.fda.gov/medwatch](http://www.fda.gov/medwatch) or call 1-800-FDA-1088.

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