Alternative Formulation Drizalma Sprinkle™

Drizalma Sprinkle™ is the first and only FDA-approved sprinkle formulation of delayed-release duloxetine—a selective serotonin and norepinephrine reuptake inhibitor designed to meet the needs of patients who cannot or will not swallow solid medication forms.

3 Administration Options for Your Patients

- Swallow whole
- Open and sprinkle over applesauce
- Open and administer via nasogastric tube

No need for crushing; just open, sprinkle, and serve

INDICATIONS AND USAGE

Drizalma Sprinkle™ (duloxetine) delayed-release capsules are indicated for the treatment of:

- Major depressive disorder in adults
- Generalized anxiety disorder in adults and pediatric patients aged 7 to 17 years
- Diabetic Peripheral Neuropathic Pain (DPNP) in adults
- Chronic musculoskeletal pain in adults

IMPORTANT SAFETY INFORMATION

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

Antidepressants increased the risk of suicidal thoughts and behavior in pediatric and young adult patients in short-term studies. Closely monitor all antidepressant-treated patients for clinical worsening and for emergence of suicidal thoughts and behaviors.

CONTRAINDICATIONS

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

Please see additional Important Safety Information throughout this journal cover wrap, and Brief Summary of Full Prescribing Information, including Boxed Warning.
Addressing an Unmet Need for Patients With Difficulty Swallowing

Depression affects more than 6.5 million (approximately 20%) of the 35 million Americans aged 65 years and older.

Approximately 40% of American adults cannot or will not swallow solid forms of medication.

Drizalma Sprinkle™ is indicated for Major Depressive Disorder (MDD) in adults.

Drizalma Sprinkle™ is indicated for Generalized Anxiety Disorder (GAD) in adults and pediatric patients aged 7 to 17 years.

IMPORTANT SAFETY INFORMATION (cont’ed)

WARNINGS AND PRECAUTIONS

- **Hepatotoxicity:** Hepatic failure, sometimes fatal, has been reported in patients treated with duloxetine delayed-release capsules. Treatment should be discontinued in patients who develop jaundice or other evidence of clinically significant liver dysfunction and should not be resumed unless another cause can be established. Drizalma Sprinkle™ should not be prescribed for patients with substantial alcohol use or evidence of chronic liver disease.
- **Orthostatic Hypotension, Falls, and Syncope:** Syncope and orthostatic hypotension tend to occur within the first week of therapy but can occur at any time during treatment, particularly after dose increases.
- **Serotonin Syndrome:** There is increased risk when coadministered with other serotonergic agents (e.g., SSRIs, SNRIs, triptans), but also when taken alone. Monitor all patients taking Drizalma Sprinkle™ for the emergence of serotonin syndrome. If it occurs, discontinue Drizalma Sprinkle™ and initiate supportive treatment.
- **Increased Risk of Bleeding:** Duloxetine may increase the risk of bleeding events. A post-marketing study showed a higher incidence of postpartum hemorrhage in mothers taking duloxetine. Concomitant use of NSAIDs, aspirin, other antiplatelet drugs, warfarin, and anticoagulants may increase this risk.
- **Severe Skin Reactions:** Severe skin reactions, including erythema multiforme and Stevens-Johnson Syndrome, can occur with duloxetine. Drizalma Sprinkle™ should be discontinued at the first appearance of blisters, peeling rash, mucosal erosions, or any other sign of hypersensitivity if no other etiology can be identified.
- **Discontinuation Syndrome:** Adverse reactions after discontinuation of serotonergic antidepressants, particularly after abrupt discontinuation, include nausea, sweating, dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias, such as electric shock sensations), tremor, anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. A gradual reduction in dosage rather than abrupt cessation is recommended whenever possible.
- **Activation of Mania or Hypomania:** In patients with bipolar disorder, treating a depressive episode with duloxetine or another antidepressant may precipitate a mixed/manic episode. Use cautiously in patients with bipolar disorder. Prior to initiating treatment with Drizalma Sprinkle™, screen patients for any personal or family history of bipolar disorder, mania, or hypomania.
- **Angle-Closure Glaucoma:** Duloxetine may trigger an angle-closure attack in patients with anatomically narrow angles who do not have a patent iridectomy. Avoid use of Drizalma Sprinkle™ in patients with anatomically narrow angles.
- **Seizures:** Drizalma Sprinkle™ should be prescribed with care in patients with a history of seizure disorder.
- **Blood Pressure:** Monitor blood pressure prior to initiating treatment and periodically throughout treatment.
- **Hyponatremia:** Can occur in association with SIADH. Cases of hyponatremia have been reported.
- **Glucose Control in Diabetes:** In diabetic peripheral neuropathic pain patients, small increases in fasting blood glucose and HbA1c have been observed.

Please see additional Important Safety Information throughout this journal cover wrap, and Brief Summary of Full Prescribing Information, including Boxed Warning.
COMMENTARY

THE CASE FOR Psychiatric Reparations

H. Steven Moffic, MD; Rahn K. Bailey, MD; Andrew J. McLean, MD, MPH; and Tom Okamoto, MD; The PRO Group (Psychiatric Reparations Opportunities)

If conversations around racism are difficult, the particular topic of reparations is difficult in the extreme. Some of the difficulty lies in how reparations are defined. The Oxford English Dictionary, for example, defines the term as “the making of amends for a wrong one has done, by paying money to or otherwise helping those who have been wronged.” In other words, how much money is enough, and what else can help?

“Reparations fundamentally is not about money—it is about justice; reparations are closely linked to mental health status, psychological well-being, and behavior.”
—Bertha Holliday, PhD, and Alberto Figueroa-Garcia, MD

CONTINUED ON PAGE 10

A Love Letter to the Patient-Physician Relationship

Nidal Moukaddam, MD, PhD

This is a love letter. It is an ode to clinical psychiatry from one psychiatrist to another, to all those who are seeing patients in hospitals, whether they are on consult teams, in emergency departments, in solo offices, or on little screens scattered around the country. All of us psychiatrists, mental health clinicians, and therapists are listening to stories, absorbing emotions, and offering patients and families reassurance and positive action. Together, we are promoting healing and recovery.

Why would someone write a love letter to their specialty? Because after 2 decades of practicing medicine, I still find the intricacies of the human mind fascinating; I have the utmost respect for my field, which beautifully combines art and science. The scientific advances in psychiatry are fast-paced and intricate, and revolutions in conceptualizing mental...
#1 PRESCRIBED ONCE-MONTHLY LONG-ACTING INJECTABLE ATYPICAL ANTIPSYCHOTIC

INVEGA SUSTENNA®

IT’S ABOUT TIME

FOR THE TREATMENT OF SCHIZOPHRENIA IN ADULTS

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

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

Clinical evidence is available in adults recently diagnosed with schizophrenia within 1 to 5 years**

INVEGA SUSTENNA® was also evaluated in 4 short-term, double-blind, randomized, placebo-controlled pivotal trials and 1 longer-term, double-blind, placebo-controlled pivotal trial²

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

Consider once-monthly INVEGA SUSTENNA® earlier in the treatment journey.

*All patients diagnosed 1 to 5 years previously with ≥2 relapses requiring hospitalization.

INDICATION

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

• Schizophrenia in adults

IMPORTANT SAFETY INFORMATION FOR INVEGA SUSTENNA® (paliperidone palmitate)

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

See full prescribing information for complete Boxed Warning.

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

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

Actor Portrayal
IMPORTANT SAFETY INFORMATION (cont'd)

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

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

Neuroleptic Malignant Syndrome (NMS): NMS, a potentially fatal symptom complex, has been reported in association with antipsychotic drugs, including paliperidone.

Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, including delirium, and autonomic instability (irregular pulse, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

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

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

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

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

If signs and symptoms of TD appear in a patient on INVEGA SUSTENNA®, drug discontinuation should be considered. However, some patients may require treatment with INVEGA SUSTENNA® despite the presence of the syndrome. In patients who do not respond to chronic treatment at the lowest dose and in shortest duration of treatment producing a satisfactory clinical response, periodically reassess the need for continued treatment.

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

Hyperglycemia and Diabetes Mellitus: Hyperglycemia and diabetes mellitus, in some cases extreme and associated with ketoacidosis, hyperosmolar coma or death, have been reported in patients treated with all atypical antipsychotics (APS). Patients starting treatment with APS who have or are at risk for diabetes mellitus should undergo fasting blood glucose testing at the beginning of and during treatment. Patients who develop symptoms of hyperglycemia during treatment should also undergo fasting blood glucose testing. All patients treated with all atypical antipsychotics should be monitored for symptoms of hyperglycemia. Some patients require continuation of antidiabetic treatment despite discontinuation of the suspect drug.

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

Weight Gain: Weight gain has been observed with atypical antipsychotic use.

Clinical monitoring of weight is recommended.

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

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

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

Hyperprolactinemia: As with other drugs that antagonize dopamine D₂ receptors, INVEGA SUSTENNA® elevates prolactin levels, and the elevation persists during chronic administration. Paliperidone has a prolactin-lowering effect similar to risperidone, which is associated with higher levels of prolactin elevation than other antipsychotic agents.

Potential for Cognitive and Motor Impairment: Somnolence, sedation, and dizziness were reported as adverse reactions in subjects treated with INVEGA SUSTENNA®.

INVEGA SUSTENNA® has the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about performing activities that require mental alertness such as operating hazardous machinery, including motor vehicles, until they are reasonably certain that INVEGA SUSTENNA® does not adversely affect them.

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

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

Drug Interactions: Strong CYP3A4/P-glycoprotein (P-gp) inducers:

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

Pregnancy/Nursing: INVEGA SUSTENNA® may cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. Advise patients to notify their healthcare professional if they become pregnant or intend to become pregnant during treatment with INVEGA SUSTENNA®.

Patients should be advised that there is a pregnancy registry that monitors outcomes in women exposed to INVEGA SUSTENNA® during pregnancy. INVEGA SUSTENNA® can pass into human breast milk. The benefits of breastfeeding should be considered along with the mother's clinical need for INVEGA SUSTENNA® and any potential adverse effects on the breastfed infant from INVEGA SUSTENNA® or the mother's underlying condition.

Commonly Observed Adverse Reactions for INVEGA SUSTENNA®:

The most common adverse reactions in clinical trials in patients with schizophrenia (≤5% and twice placebo) were injection site reactions, somnolence/sedation, dizziness, akathisia and extrapyramidal disorder.

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

cp-64200v3

REFERENCES:

1. IQVIA Real World Data. Longitudinal Prescription (Rx) and Medical Claims (Dx) in schizophrenia in adults; April 2020–March 2021.

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

Brief Summary Before Prescribing INVEGA SUSTENNA®, Please See Full Prescribing Information, Including Boxed Warning.

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

INDICATIONS AND USAGE (INVEGA SUSTENNA® is indicated for the treatment of:

- Schizophrenia [see Clinical Studies (14.1) in Full Prescribing Information].
- Schizophrenia in adults as monotherapy and as an add-on to mood stabilizers or antidepressants [see Clinical Studies (14.2) in Full Prescribing Information].

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

WARNINGS AND PRECAUTIONS Increased Mortality or Morbidity in Elderly Patients with Dementia-Related Psychosis Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Elderly patients with dementia related psychosis treated with antipsychotics have a risk of death that is elevated over that in dementia patients not exposed to antipsychotics. The risk of death in drug-treated patients was about 2.5 times the rate of placebo-treated patients (both risk with paliperidone palmitate and risperidone; 2.6 times with paliperidone palmitate). The risk was increased to approximately 2.1 times the rate of placebo in patients taking other antipsychotics. The risk was highest in cholesterol lowering drugs (0.6% with placebo vs. 4.7% mortality in the drug group).

Antipsychotic drugs, in general, have been shown to cause mortality in elderly patients with dementia and cause or exacerbate the risk of strokes, which may be fatal. There was an increased risk of mortality in elderly patients with dementia treated with antipsychotics compared to those treated with placebo (41% vs. 27%). The risk was highest in the 80- to 89-year-old age group and for patients with a history of congestive heart failure. The risk of mortality was highest within the first year of treatment for antipsychotic drugs and continued through the study period, even at low doses. The risk may be greater for older patients (≥65 years) than for younger patients and for patients with a history of clinical conditions associated with increased mortality, particularly vascular conditions. Betah blockers, which should be used with caution in patients with coronary artery disease, were more frequent in patients treated with antipsychotics (20.3% vs. 11.6%). Patients with dementia or other cognitive impairment have a relatively high risk of falling. Antipsychotics, which may impair thinking and motor function, can increase the risk of falling, which, in the elderly, may further increase the risk of fractures and other injurious outcomes.

INVEGA SUSTENNA® is not approved for use in patients with dementia-related psychosis.
| Clinical Studies (14.1) | elevations of prolactin to above the reference range (> 13.13 ng/mL in males and > 26.26 ng/mL in females) were noted in a higher percentage of patients in the INVEGA SUSTENNA® group than those in the placebo group (5.8% vs. 0.9% and in males vs. 4.2%, vs. 0.9% during the double-blind phase, 4 females (2.4%) in the INVEGA SUSTENNA® group experienced potentially prolactin-related adverse reactions (amenorrhea N=2; galactorrhea N=2), while 2 females (1.4%) in the placebo group experienced potentially prolactin-related adverse reactions (amenorrhea N=1; breast pain N=1). One male (0.8%) in the INVEGA SUSTENNA® group experienced erectile dysfunction and 1 male (0.8%) in placebo group experienced gynecomastia.

Prior to the double-blind phase (during the 21-week open-label phase of the long-term maintenance trial), the mean (SD) serum prolactin values at baseline were 14.9 (23.3) ng/mL in INVEGA SUSTENNA®-treated males and 46.4 (71.4) ng/mL in females (N=301). During the open-label phase 48.9%, of females and 47.7% of males experienced elevations of prolactin above the baseline of at least 50% and a higher proportion of females experienced potentially prolactin-related adverse reactions compared to males (5.3% vs. 1.1%). Of the patients who had a baseline prolactin level above the reference range, 5.3% of males and no single potentially prolactin-related adverse reaction in males were observed with a rate greater than 2%.

Schizophrenic Disorder

In a long-term maintenance trial of INVEGA SUSTENNA® in schizophrenic patients (Study PSY-2001), see Clinical Studies (14.1), elevations of prolactin to above the reference range (≥ 18 ng/mL in males and ≥ 36 ng/mL in females) were noted in a higher percentage of the patients in the INVEGA SUSTENNA® group than those in the placebo group (10.4% vs. 0.9% and in males vs. 26.4%, vs. 0.9%). During the double-blind phase, 4 females (2.4%) in the INVEGA SUSTENNA® group experienced potentially prolactin-related adverse reactions (amenorrhea N=2; galactorrhea N=2), while 2 females (1.4%) in the placebo group experienced potentially prolactin-related adverse reactions (amenorrhea N=1; breast pain N=1). One male (0.8%) in the INVEGA SUSTENNA® group experienced erectile dysfunction and 1 male (0.8%) in placebo group experienced gynecomastia.

Prior to the double-blind phase (during the 21-week open-label phase of the long-term maintenance trial), the mean (SD) serum prolactin values at baseline were 14.9 (23.3) ng/mL in INVEGA SUSTENNA®-treated males and 46.4 (71.4) ng/mL in females (N=301). During the open-label phase 48.9%, of females and 47.7% of males experienced elevations of prolactin above the baseline of at least 50% and a higher proportion of females experienced potentially prolactin-related adverse reactions compared to males (5.3% vs. 1.1%). Of the patients who had a baseline prolactin level above the reference range, 5.3% of males and no single potentially prolactin-related adverse reaction in males were observed with a rate greater than 2%.

Potential for Cognitive and Motor Impairment

Somnolence, sedation, and dizziness were reported as adverse reactions in subjects treated with INVEGA SUSTENNA® (Study SCA-3004), see Clinical Studies (14.2), elevations of prolactin to above the reference range (≥ 13.1 ng/mL in males and ≥ 26.2 ng/mL in females) were noted in a higher percentage of the patients in the INVEGA SUSTENNA® group than those in the placebo group (5.8% vs. 0.9% and in males vs. 4.2%). During the double-blind phase, 4 females (2.4%) in the INVEGA SUSTENNA® group experienced potentially prolactin-related adverse reactions (amenorrhea N=2; galactorrhea N=2), while 2 females (1.4%) in the placebo group experienced potentially prolactin-related adverse reactions (amenorrhea N=1; breast pain N=1). One male (0.8%) in the INVEGA SUSTENNA® group experienced erectile dysfunction and 1 male (0.8%) in placebo group experienced gynecomastia.

Prior to the double-blind phase (during the 21-week open-label phase of the long-term maintenance trial), the mean (SD) serum prolactin values at baseline were 14.6 (14.8) ng/mL in males (N=351) and 39.1 (14.8) ng/mL in females (N=302). At the end of the open-label phase, mean (SD) prolactin values were 28.0 (17.2) ng/mL in males (N=227) and 72.4 (46.5) ng/mL in females (N=239). During the open-label phase 48.9%, of females and 47.7% of males experienced elevations of prolactin above the baseline of at least 50% and a higher proportion of females experienced potentially prolactin-related adverse reactions (amenorrhea N=2; blood prolactin increased N=1; libido decreased N=1; amenorrhea N=2; palpitations N=4), while 5 females (0.8%) and 3 males (0.5%) experienced potentially prolactin-related adverse reactions (amenorrhea N=2; blood prolactin increased N=1; amenorrhea N=2; galactorrhea N=1). Six males (1.1%) in INVEGA SUSTENNA®-treated subjects experienced potentially prolactin-related adverse reactions (hyperprolactinemia N=4; libido decreased N=1; erectile dysfunction N=1), while 1 male (1.1%) in the placebo group experienced adverse reaction of blood prolactin increased.

Prior to the 15-month double-blind phase (during the 25-week open-label phase of the long-term maintenance trial), the mean (SD) serum prolactin values at baseline were 14.6 (14.8) ng/mL in males (N=351) and 39.1 (14.8) ng/mL in females (N=302). At the end of the open-label phase, mean (SD) prolactin values were 28.0 (17.2) ng/mL in males (N=227) and 72.4 (46.5) ng/mL in females (N=239). During the open-label phase 48.9%, of females and 47.7% of males experienced elevations of prolactin above the reference range relative to baseline, and a higher proportion of females experienced potentially prolactin-related adverse reactions (amenorrhea N=2; blood prolactin increased N=1; libido decreased N=1; erectile dysfunction N=1), while 1 male (1.1%) in the placebo group experienced adverse reaction of blood prolactin increased.

Seizures

The four fixed-dose double-blind placebo-controlled studies in subjects with schizophrenia, <1% (1/128) of subjects treated with INVEGA SUSTENNA® in the recommended dose range of 39 mg to 234 mg experienced an adverse event related to convulsion compared with <1% (1/505) of placebo-treated subjects who experienced an adverse event of grand mal convulsion.

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

Neoplasms

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. INVEGA SUSTENNA® should be used cautiously in patients who are vulnerable to hypotension.

In a long-term maintenance trial of INVEGA SUSTENNA® in schizophrenic patients (Study PSY-2001), see Clinical Studies (14.1), elevations of prolactin to above the reference range (≥ 18 ng/mL in males and ≥ 36 ng/mL in females) were noted in a higher percentage of the patients in the INVEGA SUSTENNA® group than those in the placebo group (10.4% vs. 0.9% and in males vs. 26.4%, vs. 0.9%). During the double-blind phase, 4 females (2.4%) in the INVEGA SUSTENNA® group experienced potentially prolactin-related adverse reactions (amenorrhea N=2; galactorrhea N=2), while 2 females (1.4%) in the placebo group experienced potentially prolactin-related adverse reactions (amenorrhea N=1; breast pain N=1). One male (0.8%) in the INVEGA SUSTENNA® group experienced erectile dysfunction and 1 male (0.8%) in placebo group experienced gynecomastia.

Prior to the double-blind phase (during the 21-week open-label phase of the long-term maintenance trial), the mean (SD) serum prolactin values at baseline were 14.6 (14.8) ng/mL in males (N=351) and 39.1 (14.8) ng/mL in females (N=302). At the end of the open-label phase, mean (SD) prolactin values were 28.0 (17.2) ng/mL in males (N=227) and 72.4 (46.5) ng/mL in females (N=239). During the open-label phase 48.9%, of females and 47.7% of males experienced elevations of prolactin above the baseline of at least 50% and a higher proportion of females experienced potentially prolactin-related adverse reactions (amenorrhea N=2; blood prolactin increased N=1; libido decreased N=1; erectile dysfunction N=1), while 1 male (1.1%) in the placebo group experienced adverse reaction of blood prolactin increased.

Seizures

The four fixed-dose double-blind placebo-controlled studies in subjects with schizophrenia, <1% (1/128) of subjects treated with INVEGA SUSTENNA® in the recommended dose range of 39 mg to 234 mg experienced an adverse event related to convulsion compared with <1% (1/505) of placebo-treated subjects who experienced an adverse event of grand mal convulsion.

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

Neoplasms

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

Pregnancy

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

Disruption of Body Temperature Regulation

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

ADVERSE REACTIONS

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

Increased mortality in elderly patients with dementia-related psychosis (see Boxed Warning and Warnings and Precautions)

Cerebrovascular adverse reactions, including stroke, in elderly patients with dementia-related psychosis (see Warnings and Precautions)

Psychotic malignant syndromes (see Warnings and Precautions)
INVEGA SUSTENNA® (paliperidone palmitate) extended-release injectable suspension, for intramuscular use

- QT prolongation [see Warnings and Precautions]
- Tardive dyskinesia [see Warnings and Precautions]
- Metabolic changes [see Warnings and Precautions]
- Orthostatic hypotension and syncope [see Warnings and Precautions]
- Falls [see Warnings and Precautions]
- Leukopenia, neutropenia, and agranulocytosis [see Warnings and Precautions]
- Hyperprolactinemia [see Warnings and Precautions]
- Potential for cognitive and motor impairment [see Warnings and Precautions]
- Seizures [see Warnings and Precautions]
- Dysphagia [see Warnings and Precautions]
- Prapism [see Warnings and Precautions]
- Disruption of body temperature regulation [see Warnings and Precautions]

Clinical Trials Experience

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

Patient Exposure

The data described in this section are derived from a clinical trial database consisting of a total of 3917 subjects (approximately 1705 patient-years exposure) with schizophrenia who received at least one dose of INVEGA SUSTENNA® in the recommended dose range of 38 mg to 234 mg and a total of 510 subjects with schizophrenia who received placebo. Among the 3817 INVEGA SUSTENNA®-treated subjects, 1293 received INVEGA SUSTENNA® in four fixed-dose, double-blind, placebo-controlled trials (one 9-week and three 13-week studies), 949 received INVEGA SUSTENNA® during the double-blind placebo-controlled period of this study (median exposure 229 days during the initial 33-week open-label phase of this study, of whom 205 continued to receive INVEGA SUSTENNA® during the double-blind placebo-controlled phase of this study [median exposure 171 days], and 1675 received INVEGA SUSTENNA® in five non-placebo controlled trials (three noninferiority active-comparator trials, one long-term open-label pharmacokinetic and safety study, and an injection site [deltoid-gluteal] cross-over trial). One of the 9-week studies included a 234 mg INVEGA SUSTENNA® initiation dose followed by treatment with either 38 mg, 156 mg, or 234 mg every 4 weeks. The safety of INVEGA SUSTENNA® was also evaluated in a 15-month, long-term study comparing INVEGA SUSTENNA® to quetiapine, a non-phenothiazine antipsychotic therapy in adult subjects with schizophrenia. A total of 226 subjects received INVEGA SUSTENNA® during the 15-month, open-label period of this study; 218 subjects received selected oral antipsychotic therapies. The safety of INVEGA SUSTENNA® was similar to that seen in previous double-blind placebo-controlled clinical trials in adult subjects with schizophrenia. The safety of INVEGA SUSTENNA® was also evaluated in a long-term study in adult subjects with schizoaffective disorder. A total of 667 subjects received INVEGA SUSTENNA® during the initial 25-week open-label period of this study (median exposure 147 days); 164 subjects continued to receive INVEGA SUSTENNA® during the 15-month double-blind placebo-controlled period of this study (median exposure 446 days). Adverse reactions that occurred more frequently in the INVEGA SUSTENNA® than the placebo group (a 2% difference or more between groups) were weight increased, nasopharyngitis, headache, hyperprolactinemia, and pyrexia.

In one of the fixed-dose, double-blind, placebo-controlled trials in subjects with schizophrenia who received injection site reactions, somnolence/sedation, dizziness, akathisia, and extrapyramidal disorder. No occurrences of adverse events reacted this trend in the long-term double-blind, placebo-controlled study in subjects with schizoaffective disorder.

Discontinuation of Treatment Due to Adverse Events: The percentage of subjects who discontinued due to adverse events in the four fixed-dose, double-blind, placebo-controlled schizophrenia trials were similar for INVEGA SUSTENNA®- and placebo-treated subjects. The percentage of subjects who discontinued due to adverse events in the open-label period of the long-term study in subjects with schizoaffective disorder was 7.5%. During the double-blind, placebo-controlled period of the trial, 218 subjects received selected oral antipsychotic therapies. The safety of INVEGA SUSTENNA® was similar to that seen in previous double-blind placebo-controlled clinical trials in adult subjects with schizophrenia. The safety of INVEGA SUSTENNA® was also evaluated in a long-term study in adult subjects with schizoaffective disorder. A total of 667 subjects received INVEGA SUSTENNA® during the initial 25-week open-label period of this study (median exposure 147 days); 164 subjects continued to receive INVEGA SUSTENNA® during the 15-month double-blind placebo-controlled period of this study (median exposure 446 days). Adverse reactions that occurred more frequently in the INVEGA SUSTENNA® than the placebo group (a 2% difference or more between groups) were weight increased, nasopharyngitis, headache, hyperprolactinemia, and pyrexia.

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

Commonly Observed Adverse Reactions:

Commonly Observed Adverse Reactions:

Table 6 lists the adverse reactions reported in 2% or more of INVEGA SUSTENNA®-treated subjects and at a higher rate than placebo. The following list does not include reactions: 1) already listed in previous tables or elsewhere in labeling, 2) initial dose injection of 234 mg followed by either 39 mg, 156 mg, or 234 mg every 4 weeks by deltoid or gluteal injection. Other dose groups (28 mg, 78 mg, and 156 mg) are from studies involving only gluteal injection. [see Warnings and Precautions].

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

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

The following list does not include reactions: 1) already listed in previous tables or elsewhere in labeling, 2) when no dose or cause was remote, 3) which were so general as to be uninformative, or 4) which were not considered to have significant clinical implications.

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

Ear and labyrinth disorders: vertigo

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

Gastrointestinal disorders: constipation, dysphagia, flatulence, salivary hypersecrecy

Immune system disorders: hypersensitivity

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

Nervous system disorders: bradykinesia, cerebrovascular accident, cognitive rigidity, convulsion, dizziness postural, drooling, dysarthria, dystonia, akathisia, hypokinesia, parkinsonism, pyramidal hyperactivity, syncope

Psychiatric disorders: insomnia, libido decreased, restlessness

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

Respiratory, thoracic and mediastinal disorders: nasal congestion

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

Demographic Differences

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

Extrapyramidal Symptoms (EPS)

Placebo data from the two double-blind, placebo-controlled, 13-week, fixed-dose trials in adult subjects with schizophrenia provided information regarding EPS. Several methods were used to measure EPS. (1) the Simpson-Angus global score which broadly evaluates parkinsonism, (2) the Barnes Akathisia Rating Scale global clinical rating score which evaluates akathisia, (3) the Abnormal Involuntary Movement Scale scores which evaluates dyskinesia, and (4) use of anticholinergic medications to treat EPS (Table 7), and (5) incidence of spontaneous reports of EPS (Table 8).

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

<table>
<thead>
<tr>
<th>Scale</th>
<th>Placebo (%)</th>
<th>INVEGA SUSTENNA® (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Percentage of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinsonisma</td>
</tr>
<tr>
<td>Akathisia</td>
</tr>
<tr>
<td>Dyskinesia</td>
</tr>
<tr>
<td>Use of Anticholinergic Medicationsb</td>
</tr>
</tbody>
</table>

a For parkinsonism, percent of subjects with Simpson-Angus total score 6 or higher at endpoint (total defined as total sum of items score divided by the number of items)
b For Akathisia, percent of subjects with Barnes Akathisia Rating Scale global score 2 at endpoint

c For Dyskinesia, percent of subjects with a score 2 on any of the first 3 items or a score 2 on two or more of any of the first 7 items of the Abnormal Involuntary Movement Scale at endpoint

The following list includes reactions: 1) already listed in previous tables or elsewhere in labeling, 2) when no dose or cause was remote, 3) which were so general as to be uninformative, or 4) which were not considered to have significant clinical implications.
Table 8: Extrapyramidal Symptoms (EPS)- Related Events by MedDRA Preferred Term – Schizophrenia Studies in Adults

<table>
<thead>
<tr>
<th>Percentage of Subjects</th>
<th>EPS Group</th>
<th>Placebo</th>
<th>39 mg (N=262)</th>
<th>78 mg (N=233)</th>
<th>156 mg (N=228)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall incidence of EPS-related adverse events</td>
<td>Parkinsonism</td>
<td>10</td>
<td>12</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Akathisia</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Dystonia</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Tremor</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Dyskinesia</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Dystonia</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 9: Clinically Important Drug Interactions with INVEGA SUSTENNA®

<table>
<thead>
<tr>
<th>Concomitant Drug Name or Drug Class</th>
<th>Clinical Rationale</th>
<th>Clinical Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>The concomitant use of carbamazepine and INVEGA SUSTENNA® has been studied in elderly patients with schizophrenia and is not associated with a higher risk of adverse reactions than that seen in the placebo group.</td>
<td>Monitor vital signs and serum INVEGA SUSTENNA® levels during treatment.</td>
</tr>
<tr>
<td>Levodopa and Other Dopamine Agonists</td>
<td>The concomitant use of levodopa and other dopamine agonists and INVEGA SUSTENNA® has been studied in elderly patients with schizophrenia and is not associated with a higher risk of adverse reactions than that seen in the placebo group.</td>
<td>Monitor vital signs and serum INVEGA SUSTENNA® levels during treatment.</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>The concomitant use of antidepressants and INVEGA SUSTENNA® has been studied in elderly patients with schizophrenia and is not associated with a higher risk of adverse reactions than that seen in the placebo group.</td>
<td>Monitor vital signs and serum INVEGA SUSTENNA® levels during treatment.</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>The concomitant use of antipsychotics and INVEGA SUSTENNA® has been studied in elderly patients with schizophrenia and is not associated with a higher risk of adverse reactions than that seen in the placebo group.</td>
<td>Monitor vital signs and serum INVEGA SUSTENNA® levels during treatment.</td>
</tr>
<tr>
<td>Valproate</td>
<td>The concomitant use of valproate and INVEGA SUSTENNA® has been studied in elderly patients with schizophrenia and is not associated with a higher risk of adverse reactions than that seen in the placebo group.</td>
<td>Monitor vital signs and serum INVEGA SUSTENNA® levels during treatment.</td>
</tr>
<tr>
<td>Monamine Oxidase Inhibitors</td>
<td>The concomitant use of monamine oxidase inhibitors and INVEGA SUSTENNA® has been studied in elderly patients with schizophrenia and is not associated with a higher risk of adverse reactions than that seen in the placebo group.</td>
<td>Monitor vital signs and serum INVEGA SUSTENNA® levels during treatment.</td>
</tr>
<tr>
<td>Lithium</td>
<td>The concomitant use of lithium and INVEGA SUSTENNA® has been studied in elderly patients with schizophrenia and is not associated with a higher risk of adverse reactions than that seen in the placebo group.</td>
<td>Monitor vital signs and serum INVEGA SUSTENNA® levels during treatment.</td>
</tr>
<tr>
<td>Alcohol</td>
<td>The concomitant use of alcohol and INVEGA SUSTENNA® has been studied in elderly patients with schizophrenia and is not associated with a higher risk of adverse reactions than that seen in the placebo group.</td>
<td>Monitor vital signs and serum INVEGA SUSTENNA® levels during treatment.</td>
</tr>
<tr>
<td>Other Drugs</td>
<td>The concomitant use of other drugs and INVEGA SUSTENNA® has been studied in elderly patients with schizophrenia and is not associated with a higher risk of adverse reactions than that seen in the placebo group.</td>
<td>Monitor vital signs and serum INVEGA SUSTENNA® levels during treatment.</td>
</tr>
</tbody>
</table>

In the long-term study in subjects with schizoaffective disorder, EPS reported during the 25-week open-label treatment were similar to those reported during the 15-month double-blind treatment. The incidence of any EPS was similar to that of the placebo group (8%) and was similar to that of the INVEGA SUSTENNA® 78 mg group (9%) and 5%, respectively. Dystonia, muscle spasms, akathisia, and parkinsonism were also observed in subjects receiving INVEGA SUSTENNA®. The mean intensity of injection pain reported by subjects using a visual analog scale (0 = no pain to 100 = unbearably painful) decreased in all treatment groups from the first to the last injection (placebo: 10.9 to 8.9; 39 mg: 10.3 to 7.7; 78 mg: 10.0 to 9.2; 156 mg: 11.1 to 8.8). The results from both the 9-week, fixed-dose, double-blind, placebo-controlled trial and the double-blind phase of the maintenance trial exhibited comparable findings.

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

- Akathisia
- Arousal disorder
- Catatonia
- Gynecomastia
- Hirsutism
- Impaired social cognition
- Impaired sexual function
- Somnolence

INVEGA SUSTENNA® (paliperidone palmitate)

INVEGA SUSTENNA® is indicated for the acute and extended-release injectable suspension, for intramuscular use.
INVEGA SUSTENNA® (paliperidone palmitate) extended-release injectable suspension, for intramuscular use

**Animal Data**

There were no treatment-related effects on the offspring when pregnant rats were injected intramuscularly with paliperidone palmitate extended-release injectable suspension during the period of organogenesis at doses up to 250 mg/kg, which is 10 times the MRHD of 254 mg paliperidone based on mg/m² body surface area. In animal reproduction studies, there were no increases in fetal abnormalities when pregnant rats and rabbits were treated orally with paliperidone during the period of organogenesis with up to 8 times the MRHD of 12 mg based on mg/m² body surface area. Additional reproduction toxicity studies were conducted with orally administered risperidone, which is extensively converted to paliperidone. Cleared fat was observed in the offspring of pregnant mice treated with risperidone at 3 to 4 times the MRHD of 16 mg based on mg/m² body surface area; maternal toxicity occurred at 4 times the MRHD. There was no evidence of teratogenicity in embryo-fetal developmental toxicity studies with risperidone in rats and rabbits at doses up to 6 times the MRHD of 16 mg/day risperidone based on mg/m² body surface area. When the offspring of pregnant rats, treated with risperidone at 0.6 times the MRHD based on mg/m² body surface area, reached adulthood, learning was impaired. Increased neuronal cell death occurred in the fetal brains of the offspring of pregnant rats treated at 0.6 to 1.2 times the MRHD; the postnatal development and growth of the offspring was delayed. In rat reproduction studies with risperidone, pup deaths occurred at oral doses which are less than the MRHD of 16 mg/day based on mg/m² body surface area; it is not known whether these deaths were due to a direct effect on the fetuses or pups or, to effects on the dams (see RISPERIDAL® package insert).

**Lactation**

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

**Clinical Considerations**

Infants exposed to INVEGA SUSTENNA® through breast milk should be monitored for excess sedation, failure to thrive, jitteriness, and extrapyramidal symptoms (tremors and abnormal muscle movements).

**Females and Males of Reproductive Potential**

**Infertility**

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

**Pediatric Use**

Safety and effectiveness of INVEGA SUSTENNA® have been established in patients < 18 years of age.

**Juvenile Animal Studies**

In a study in which juvenile rats were treated with oral paliperidone from days 24 to 73 of age, a reversible neurobehavioral impairment in a test of learning and memory was seen in females only, with a no-effect dose of 0.63 mg/kg/day, which produced plasma levels (AUC) of paliperidone similar to those in adolescents dosed at 12 mg/day. No other consistent effects on neurobehavioral or reproductive development were seen up to the highest dose tested (2.5 mg/kg/day), which produced plasma levels of paliperidone 2-3 times those in adolescents.

Juvenile dogs were treated for 80 weeks with oral risperidone, which is extensively metabolized to paliperidone in animals and humans, at doses of 0.31, 1.25, or 5 mg/kg/day. Decreased bone length and density were seen with a no-effect dose of 0.31 mg/kg/day, which produced plasma levels (AUC) of risperidone plus paliperidone which were similar to those in children and adolescents receiving the MRHD of risperidone. In addition, a delay in sexual maturation was seen at all doses in both male and females. The above effects showed little or no reversibility in females after a 12-week drug-free recovery period. The long-term effects of INVEGA SUSTENNA® on growth and sexual maturation have not been fully evaluated in children and adolescents.

**Geriatric Use**

Clinical studies of INVEGA SUSTENNA® did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

This drug is known to be substantially excreted by the kidney and clearance is decreased in patients with renal impairment (see Pharmacokinetics (12.3) in Full Prescribing Information) and Clinical Pharmacology (12.3) in Full Prescribing Information). Therefore, dosage adjustment is needed in these patients.

**Renal Impairment**

INVEGA SUSTENNA® is not recommended in patients with moderate or severe renal impairment (creatinine clearance < 50 mL/min). Dose reduction is recommended for patients with mild renal impairment (creatinine clearance > 50 mL/min to < 80 mL/min) [see Dosage and Administration (2.5) and Clinical Pharmacology (12.3) in Full Prescribing Information].

**Hepatic Impairment**

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

**Patients with Parkinson’s Disease or Lewy Body Dementia**

Patients with Parkinson’s Disease or Lewy Body Dementia have an increased risk of dyskinetic movements which could be worsened by the use of antipsychotic drugs. Consider the use of other drugs with a lower risk of these movements prior to the use of paliperidone.

**Drug Abuse and Dependence**

**Controlled Substance**

INVEGA SUSTENNA® (paliperidone palmitate) is a controlled substance (Schedule V).

**Abuse**

Paliperidone has not been known to be abused or diverted for non-medical use.

**Dependence**

Paliperidone has not been known to be physically or psychologically dependent on paliperidone.

OVERDOSAGE

**Human Experience**

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

While experience with paliperidone overdose is limited, among the few cases of overdose reported in premarketing trials with oral paliperidone, the highest estimated ingestion was 406 mg. Observed signs and symptoms included extrapyramidal symptoms and gait unsteadiness. Other potential signs and symptoms include those resulting from an exaggeration of paliperidone’s known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypertension, and QT prolongation. Torsades de pointes and ventricular fibrillation have been reported in a patient in the setting of overdose with oral paliperidone.

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

**Management of Overdose**

Avoiding a second dose of INVEGA SUSTENNA® in patients after overdose is recommended.

**Product of Ireland**

Manufactured by:

Janssen Pharmaceutical Companies

Janssen Pharmaceuticals, Inc.

Titusville, NJ 08560

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cp-9015v2

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

Product of Ireland

Manufactured by:

Janssen Pharmaceutical Companies

Janssen Pharmaceuticals, Inc.

Titusville, NJ 08560

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cp-9015v2
Questions Linger About COVID-19’s Origin

Was it a natural zoonotic spillover that catalyzed SARS-CoV-2 from an emerging virus into a pandemic pathogen or was it something much more sinister? Did a lab leak in Wuhan, China, cast a spark that lit the fuse?

Debate and discussion about the origin of the virus that causes COVID-19 have been at the forefront of the global consciousness since the first cases were reported in December 2019.

Early on, whispers of a potentially engineered virus quickly grew to a roar and fueled speculation that China was behind the pandemic. This narrative was so pervasive that, in February 2020, 27 public health scientists published a letter in *The Lancet* disputing the lab leak theory and announcing their support of their counterpart’s claims in China: the scientists, public officials, and medical professionals combating the pandemic.

The authors, who all declared no competing interests in their disclosures, wrote: “We stand together to strongly condemn conspiracy theories suggesting that COVID-19 does not have a natural origin.”

And although analyses of the genomic sequence of the virus subsequently pointed to natural origins, the questions regarding China’s role persisted, led by discrepancies and conflicting reports.

Fast forward to June 2021, when new evidence breathed new life into the origin theories. *The Lancet* published an addendum with revised disclosure statements from virologist and investigator Peter Daszak, PhD, one of the 27 authors of the original letter: it noted that Daszak’s remuneration is paid solely in the form of a salary from EcoHealth Alliance, a New York-based nonprofit research foundation of which he is president. The company has reportedly worked directly with Wuhan laboratories and funded gain-of-function research at China’s Wuhan Institute of Virology.

Consider, too, other odd associations. Recent reports have uncovered financial ties between Google and EcoHealth Alliance. This comes after accusations that the tech giant censored lab leak conspiracy theory stories in its search results. Google has dismissed those reports, insisting the company is simply taking steps to protect users from unverified information.

Are these coincidences or is this a case of “where there’s smoke, there’s fire”? Although the answer is unclear, these questions add to the bank of other troublesome queries standing in the way of the truth about COVID-19.

The questions extend beyond origin theory. After the US Food and Drug Administration, approved the vaccine use for adolescents, a new concern arose over its long-term effects, especially on fertility and heart inflammation. Robert Malone, MD, the inventor of the mRNA technology, recently expressed strong concern over the risk-benefit analysis of vaccination for young adults. Similarly, the Centers for Disease Control and Prevention’s Advisory Committee on Immunization Practices met to discuss instances of myocarditis or pericarditis in individuals aged 30 and younger who have received an mRNA COVID-19 vaccine.

Of course, we may never know the answers to these and other questions. And that, right now, is the only answer that matters.
**FROM THE EDITOR**

**Cannabis Confusion**

John J. Miller, MD | Editor in Chief

Prior to my decision to attend medical school, I was planning to become a basic science researcher. I studied biochemistry in college at a time when it was a relatively young field. My bachelor of science curriculum included 7 semesters of chemistry; 5 semesters of biochemistry, physics, microbiology, and zoology; and a senior honors thesis that entailed designing, completing, and defending a novel research project. I successfully defended my thesis, “An Analysis of the Fate of the Escherichia coli 4.5S RNA Gene in Yeast Using a Recombinant Plasmid,” and was planning to attend graduate school in genetics at the University of Washington in Seattle.

Between completing my senior thesis and my planned move to Seattle, I suddenly panicked and wondered: Is this truly the career path for me? Ultimately, I realized I did not have what it took to be a basic science researcher, so I worked for a year as a biochemical technician and applied to medical school—a decision I have never regretted.

Yet, I do not regret my background in biochemistry either. It is the foundation upon which all I have learned of medicine and psychiatry is built. The field of neuropsychopharmacology has evolved over the past 30 years, and I am filled with pride, awe, and excitement to have witnessed the clinical advances that basic science researchers have made possible. However, in my opinion, there is a significant exception to all my accolades for how good science has advanced medicine: the research on cannabis.

The scientific method is used in medicine and has been the established paradigm for scientific inquiry since the 1600s. Thus, clinical trials submitted to the US Food and Drug Administration (FDA) are meticulously designed to answer a primary outcome question about the drug under investigation. A necessary requirement of the study design is to ensure that the variables in the various arms of the study are identical except for one: drug A at dose X compared with placebo. If multiple doses of drug A or multiple drugs are being compared, each arm is precisely characterized so the conclusions drawn from the primary outcome will be highly accurate and reliable.

**Components of Cannabis**

Over the past 10 years, I have read numerous articles in the psychiatric literature that draw conflicting conclusions about the effects of cannabis on cognition, its attendant risk of psychosis, its addictive potential, and its effect on suicidality, and about its impacts on depression, anxiety, pain relief, and apathy. There appears to be only 1 consistent finding: Heavy cannabis use during brain development increases the risk of psychosis and cognitive impairment, especially when other risk factors are present. A likely explanation for the wide-ranging discrepancies is that cannabis is the product of a plant that is not a single molecule or pure substance. Many articles with the word cannabis in the title can be discarded as...
meaningless unless the authors took the additional step of testing all of the cannabis used by their study subjects for the quantitative and qualitative molecules present.

It is well established that cannabis contains more than 500 unique molecular constituents. These constituents include more than 100 cannabinoids, more than 200 terpenoids (terpenes), and numerous flavonoids. Two cannabinoid acids are most prevalent in cannabis: Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD), both of which exist in an extremely wide range of ratios depending on the specific strain of cannabis assayed. Significantly, these 2 cannabinoids are positional in their clinical effects and have dramatically different pharmacodynamic effects. In reviewing the literature on cannabis, a consistent finding is that potency of cannabis is a proxy for the amount of THC. Although this is likely a result of the psychoactive effects of cannabis that have been noted for more than 6000 years, CBD has surfaced as an important cannabis component with many positive medicinal properties. Notably, cannabis remains a Schedule 1 drug by the Drug Enforcement Administration (DEA), while CBD is unscheduled.

The Table documents some of the significant differences between THC and CBD. Despite these differences, the vast majority of publications on cannabis draw conclusions based on participants’ self-reports of quantity and frequency of cannabis use. In these studies, the molecular components of the cannabis used are not known, nor is the important ratio of THC to CBD.

A fair analogy would be to evaluate a new drug; let us call it Sedalant. Sedalant contains a wide-ranging ratio of 2 molecules with different mechanisms of action: one a sedative, and one a stimulant. Without knowing the exact ratios and concentrations of each of these molecules in clinical studies of Sedalant, no evidence-based conclusions could be drawn from the drug studies.

Naturally occurring cannabis plants produce roughly an equal ratio of THC to CBD, containing approximately 2% of each. However, over the decades, with selective breeding in some strains, THC has been increased significantly while CBD has been virtually bred out. Therefore, it would be reasonable to assume that THC and CBD are present in different strains.

Interestingly, the odds (skunk is a common description) often associated with cannabis are largely due to the complex combination of terpenes, another compound that complicates the study of cannabis. (Cannabinoids are odorless.) An extensive literature documents the essential role terpenes play in the biology of the cannabis plant, the plant’s production of cannabinoids, and the properties of a specific strain of cannabis that help determine its market value. Terpenes likely also contribute pharmacodynamic and pharmacokinetic effects that impact the neuropsychopharmacology resulting from ingestion of each different strain of cannabis.

Several publications since 2018 have appropriately concluded that we know very little about the range of pharmacological effects from cannabinoids due to the large variability of cannabinoids, terpenes, and flavonoids that are present in different strains. If multiple strains are used in a clinical trial, they should be analyzed (as noted in Table) as a single strain in each study; each strain used should be analyzed quantitatively and qualitatively for biologically active components.

Future Research

With each passing year, more US states legalize cannabis for medical use, recreational use, or both. It is likely that federal laws will eventually make cannabis use legal on a national level. That will create an opportunity to require a comprehensive analysis and disclosure of all the components of the numerous strains of cannabis currently being sold in state dispensaries or on the streets. Concurrently, the individual molecular components of the cannabis plant should be identified and pharmacologically characterized. This would create a treasure trove of possible drug candidates for specific clinical indications, and it would allow for a more informed choice when choosing a cannabis product.

In this scenario, cannabis should be regulated federally similar to tobacco products and alcohol. Both of these have significant risks, and both are tightly controlled. Ideally, the taxes imposed on federally regulated cannabis could help fund the extensive research needed to allow a more competent understanding of the complex combination of molecules that different strains of cannabis contain.

### Table. Comparison of Properties of THC and CBD

<table>
<thead>
<tr>
<th>Property</th>
<th>THC</th>
<th>CBD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannabinoid 1 receptor</td>
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</tr>
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<td>No activity</td>
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</tr>
<tr>
<td>Psychosis</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Anxiety</td>
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<td>↓</td>
</tr>
<tr>
<td>Short-term memory impairment</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Distortion of time</td>
<td>Significant</td>
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</tr>
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</tr>
<tr>
<td>Cytochrome P450 3A4</td>
<td>Substrate/possible inhibitor&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Substrate&lt;sup&gt;12&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cytochrome P450 2C9</td>
<td>Substrate/possible inhibitor&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Low inhibition&lt;sup&gt;12&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cytochrome P450 2C19</td>
<td>No activity&lt;sup&gt;12&lt;/sup&gt;</td>
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</tr>
<tr>
<td>DEA status</td>
<td>Schedule 1</td>
<td>Unscheduled</td>
</tr>
<tr>
<td>FDA approved</td>
<td>No</td>
<td>Yes</td>
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</table>

CONCLUSION

CBD, cannabidiol; DEA, Drug Enforcement Administration; THC, Δ9-tetrahydrocannabinol.

CBD cannabis should be regulated similarly to alcohol and tobacco products.

Cannabis should be federally legalized and regulated similarly to alcohol and tobacco products.

Cannabis should not be regulated by the FDA due to its extreme heterogeneity of components and the associated unpredictable pharmacological properties.

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CBD, cannabidiol; DEA, Drug Enforcement Administration; THC, Δ9-tetrahydrocannabinol.

For this very reason, it would be contrary to the scientific method of research to attempt to gain FDA approval of cannabis.

Only 1 of the more than 100 cannabinoid components in cannabis has been sufficiently studied to receive FDA approval: CBD. Following a comprehensive analysis as well as clinical trials of pure CBD, it received approval in 2018 for the treatment of seizures in Dravet syndrome and in Lennox-Gastaut syndrome in children and adults. We may see additional approvals in the future for this well-studied compound, as a growing and consistent body of evidence shows that pure CBD in defined dosages has antipsychotic effects in patients with schizophrenia.

The practice of medicine is built upon evidence-based treatments that have been appropriately vetted by well-established protocols. CBD traveled this path to become an FDA approved drug, and so should any other component of the 500-plus molecules in cannabis. Accordingly, clinical publications should be held to a higher standard of identifying and defining what components of cannabis are relevant in any article being submitted for publication.

### 10 Recommendations

1. The word cannabis should not be used casually in medical literature, as it is nonspecific and includes varying molecular combinations of diverse cannabinoids, terpenes, and flavonoids.

2. Future research involving cannabis should use a single strain in each study; each strain used should be analyzed quantitatively and qualitatively for biologically active components.

3. If multiple strains are used in a clinical trial, they should be analyzed (as noted in Table) as a single arm compared with placebo.

4. Increased funding is needed to accurately characterize the 500-plus molecular components of the cannabis plant, including the pharmacokinetics and pharmacodynamics of each component.

5. A public education campaign should progressively disseminate the molecular facts about cannabis, especially the oppositional effects of THC and CBD. Similarly, the risks of increased psychosis and cognitive impairment with heavy regular use of THC in the developing brain should be explained, much like disclaimers on alcohol about drinking during pregnancy.

6. Cannabis should be federally legalized and regulated similarly to alcohol and tobacco products.

7. Cannabis should not be regulated by the FDA due to its extreme heterogeneity of components and the associated unpredictable pharmacological properties.

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</table>
The Case for Psychiatric Reparations

Continued from Cover

For instance, as an “otherwise” form of help, does affirmative action qualify as reparations? Affirmative action has been used for the past half century to encourage the success of African Americans in particular. It is a policy designed to make amends for their underrepresentation in workplaces, contracts, and education admissions. Over the years, affirmative action expanded to cover many kinds of differences in a commitment to diversity. That diversity could include severely ill psychiatric patients who encountered stigma and other obstacles to recovery. The policy has also helped White women, perhaps the most out of any groups. However, it is currently of concern for its use as a means of discriminating against Asian American college applicants. Along with the dramatic success of Asian Americans in admission to and performance in college, a form of backlash has emerged, such as the claim that Harvard has recently been manipulating their admissions process against Asian Americans.

On June 17, 2021, President Biden signed the Juneteenth National Independence Day Act into law, making June 19th a federal holiday commemorating emancipation. Of course, it does not contain any particular financial reparations, but it may provide a measure of moral and psychological reparations. It will update our Declaration of Independence, commemorated on July 4th, because that declaration was not fully inclusive of African Americans or women. Nationally celebrating July 4th alone may be an example of unintentional hidden structural racism; Juneteenth can chip away at that. What a formal societal step forward this is from June 19, 1865, when General Granger arrived in Galveston to notify slaves that the Civil War was over and that they were free—of course, this came more than 2 years after President Abraham Lincoln signed the Emancipation Proclamation.

“Without internal growth, we are encumbered with the destructiveness of projecting our own faults upon others and doomed to an unlimited appetite for revenge.”

From the psychiatric perspective, making amends would refer to supporting the mental health of the victims in any way possible, including the provision of physical and mental health care. Health, education, and child development services would therefore need improvement. Moreover, making amends seems to overlap or follow forgiveness, a psychological process that can help both the perpetrator and the victim. A clear example of that might be the man-made traumas of posttraumatic stress disorder, for which the perpetrator(s) made enough amends to help the victim, say, in a sexual abuse case, and the victim conveyed some forgiveness.

In the United States, the societal discussion about reparations seems to focus on African Americans. However, as with affirmative action, it can pertain to other races, cultural groups, or populations across the globe. In the United States, there are groups that could convincingly claim they have been historically wronged by our government, including Native Americans, who have been wronged since the arrival of Europeans, as well as Japanese Americans, who were interned during World War II. Chinese Americans, who were not properly treated in the latter half of the 1800s, and Jews, many of whom were denied entry during the Holocaust, might also have a case. Not only have these groups suffered historical wrongs, they are still experiencing wrongs, as conveyed in the current discrimination that African Americans, Native Americans, Asian Americans, and Jewish Americans face. Resistance to reparations is common and may reflect the reluctance to accept practical responsibility for something in the past, as well as to avoid feeling worthy of blame and shame.

It seems psychiatry rarely addresses reparations. In fact, it was not mentioned in the recent apology for racism actions offered by the American Psychiatric Association. However, the psychoanalyst Melanie Klein mentioned reparations about a century ago, describing it as instrumental to the early developmental process. Infants could even unwittingly provide psychological reparations to the mother when they soften their inevitable angry outbursts with ensuing smiles of satisfaction. By extrapolation, reparations can be applied in later life from small gestures up to systemic amends.

This article will try to make amends for the psychiatric neglect, lack of education, and limited activism on racism and its danger to public mental health.

African American Reparations

Rahn Bailey, MD

Reparations for the damage of slavery began at the end of the Civil War in 1865 with General William Tecumseh Sherman’s order to redistribute acres of land—as the mythical 40 acres and a mule—to newly freed African American families. However, President Andrew Johnson overturned this order. Nothing more happened for 100 years. Recent efforts have been stopped and started, and have often been polarizing. Although our country’s founding principles of equality, opportunity, and freedom have been eloquently promulgated, they are applied in a markedly different way for people, especially African Americans.

More than 4 centuries of harm has resulted in structural racism, institutional racism in organizations, and conscious or unconscious individual racism in America. With intergenerational transmission of trauma, fueled by epigenetic vulnerability and recurrent triggers of historical and current trauma, the collective and individual psychiatric damage must be significant.

There is a wide divide between White and African Americans in terms of health, success, and prosperity. A small number of African Americans have achieved great success in the United States, mostly in the public eye of entertainment, sports, and government (e.g., President Barack Obama). This fact has often been used as a counterargument to the disparities. Of course, these successes are the exception, not the rule.

The financial aspect of reparations tends to be the most controversial. Some scholars have devised a figure for the current descendants of slavery and ensuing discrimination. One example is the 1973 rough price tag, which was determined by multiplying the number of African Americans in the population by the difference in White and Black per capita income. However, reparations do not solely, or mainly, need to be in the form of monetary compensations.

A variation on financial reparations has emerged in Evanston, Illinois—the first city in the United States to approve reparations for Black residents. The plan is to use tax money from recreational marijuana sales to award $25,000 for home repairs, down payments on property, and interest or late penalties on property in the city. Eligible individuals include those who lived in or are a descendant of a Black individual who lived in Evanston between 1919 and 1969, who suffered discrimination as a result of housing policies. This plan fails to account for psychological amends, and some Black leaders are critical, mostly because they were not part of the decision-making process. They further see it as more of a housing plan than reparations.

In psychiatry, specifically, the need for reparations can be demonstrated in academic psychiatry. Some progress has been made in this area, with African American female psychiatrists serving in leadership roles. However, those roles seem to come too often with inadequate funding and power, which in turn contributes to limited success and substantial stress for these leaders.

This is a clear example in which reparations funding and adequate authority could lead to more opportunities that would ripple out to other faculty, the education of future psychiatrists, and improved patient care for diverse populations.
Indigenous (Native) Americans Reparations

Andrew McLean, MD, MPH

Indigenous Americans, including American Indians and Alaska Natives, have been wronged by government and institutional colonialism. These wrongs include broken treaties and forced migrations to land that was often unsuitable for habitation or development.

A century ago, our own profession sanctioned Indian insane asylums, where individuals would be committed with such dubious disorders as horse-stealing mania. So-called Indian Residential Schools were built under the guise of providing education, and discouraged or banned Native culture and language. Inevitably, historical traumas remain interwoven with individual traumas, although they can vary among the 574 federally recognized tribes. More loss and trauma have occurred more recently, as Indigenous Americans have been hospitalized with COVID-19 at 5 times the rate of White Americans. The mental health of Indigenous Americans has suffered for decades, and the population has a high rate of incarceration. The marginalization (geographically, socially, or otherwise) of any group allows discrimination to flourish, which has been the case for Indigenous Americans.

Occasionally, reparations have been given in the form of land, cash, tax relief, and other measures, which include those taken by the Indian Claims Commission of 1946 and the Alaska Native Claims Settlement Act of 1971. Former senators Sam Brownback, JD, and Byron Dorgan, MBA, proposed a stand-alone Native American Apology Resolution in Congress in 2009, but that effort failed. Instead, in what felt like a rather disingenuous approach, an unheralded Congressional apology was tucked away on page 45 of an unrelated military spending bill, with legalese indicating that it was not meant to support any claims against the government. President Obama, however, publicly acknowledged the apology.

Some governments and institutions have committed to partnering with Indigenous Peoples, engaging in positive movement. For almost 50 years, the University of North Dakota has ensured that roughly 10% of its medical school admissions are comprised of American Indian/Alaska Native individuals. The university has also developed the first Indigenous Health PhD program in the world.

Even when financial reparations are provided, they may not change cultural narratives and mindsets, as transgressions can still be denied. For Indigenous Americans, telling, hearing, and acknowledging the truth has yet to occur. The fact that many tribes have leveraged their sovereignty to develop robust, Native-owned businesses and cultural programs does not pardon institutions from the responsibility of reparations.

Japanese American Reparations

Thomas Okamoto, MD

Calls for reparations often refer to the Japanese American World War II internment and its redress movement, which culminated in the Civil Liberties Act of 1987. After an 18-year process filled with tious differences of opinion, the fact-finding commission found no basis for what it called “pressing public necessity,” and that “race prejudice, war hysteria, and a failure of political leadership” had led to President Franklin D. Roosevelt’s Executive Order 9066. Beginning in 1990, each surviving Japanese American citizen was awarded $20,000 in compensation. Despite its apparent success, many Japanese Americans were left bitter and frustrated. They viewed Japanese American legislators, attorneys, and others working within the system as accommodating the government’s institutional racism. Collective efforts supported the negotiations for eventual reparations, but they did not stop hate-inspired crimes against surviving internees and their descendants. The efforts did not erase lost generational wealth, or the continued emotional pain. In other words, financial reparations did not transform racism against Japanese Americans.

Psychiatry can direct the discussion on reparations toward the intrapsychic world. Psychiatrists can see othering and the process of racism as regressive expressions of unconscious defenses, including splitting and projection. These necessary early functions in development promote a successful negotiation of our own good and bad internal world.

Perhaps the most healing part of the Civil Liberties Act of 1987 was not the restitution, but the validation of injustice and the promotion of community grieving. In recorded public testimonies, survivors and their descendants heard internees verbalize the descriptions of their experiences for the first time, including shared loss and pain. This process reawakened painful memories that had been suppressed for decades. In a culture biased by gaman (perseverance with dignity) and shikata ga nai (it cannot be helped), the testimonies initiated the sharing of grief, thereby beginning the intrapsychic healing for this trauma.

Climate Reparations

H. Steven Moffic, MD

In these interconnected global times, a new conception applies to the current climate crisis.

The instability of our climate has caused harm in various countries and sometimes simultaneously around the world. For instance, the cold and snow unexpectedly hit Texas in February 2021 and also caused canals to freeze in Amsterdam. Although there are calls for the development of transformational resilience and mitigation in at-risk communities, there may not be funds to do so in poor communities. Hence, some individuals become climate refugees, with all the mixed and ambivalent responses of potential host countries.

Climate reparations could provide amends for both past climate destruction as well as unborn future generations. Even with reduced carbon emissions, climate damage will continue for decades. The question of reparations is more challenging. In addition to the guilt of corporations—some of whom have hidden the risk and abuses for decades—and governments, how much is each individual to blame? A systemic approach to redistributing resources may be the solution. Perhaps countries and corporations with the most carbon pollution could contribute to international reparative funds to even out inequities in resilience capability. Such a comprehensive past, present, and future approach may also help to reduce undue anticipatory anxiety and pretraumatic stress in the most at-risk populations.
Recommendations

Although reparations are usually thought of in terms of financial amends to large populations and systems, they can be gestures provided on a spectrum from the small to the global. Given the ubiquity of micro-aggressions toward Black Americans and others, a smile, an apology, and a change in behavior by the perpetrator can have everyday psychological reparative recurrences.

However, in terms of our society, making amends is urgent. Why? Throughout history, epidemics have tended to intensify social inequities, and we are in a pandemic.21

Psychological reparations clearly make a difference and can be put into motion quickly if psychiatric systems recognize the need to do so. One example would be assessing and responding to disparities in patient care and staff composition.

It could be argued that psychological reparations are the essence of any kind of reparations. Financial reparations, besides any needed practical reparations, can increase feelings of self-worth because the individual and group are deemed worthy of the cost.22 On the other hand, financial reparations alone can feel tainted, like a buyout resulting from guilt. Moreover, financial reparations may be time limited, whereas self-worth is likely to be more deeply satisfying and transmittable to others.

In psychiatry, we have most control over psychological reparations. As is done for any patient care issue and disaster response, a tentative standardization of practicalities needs to be established. For starters, we need a psychiatric reparations history (Table 1). This history can be applied to any given individual and any given system. After obtaining the history, interventions are necessary and possible (Table 2). For instance, the German government continued its reparations to Holocaust survivors by providing $135 million to help them get to COVID-19 vaccination sites around the world. This is an example of adressing trauma triggers by providing medical and psychological relief.

Without internal growth, we are encumbered with the destructiveness of projecting our own faults upon others and doomed to an unlimited appetite for revenge and retaliation, rather than acknowledging the common bond of mutual inner struggle toward loving the other. Successful psychological reparations require both community and intrapsychic reconciliation, beyond splitting and projection, entitlement, and retaliation. The process will require transformative leadership, provided by leaders from the wronged group. Finding commonality and diverse aliyshp is necessary for the healing of past trauma and for positive movement.

Psychological and other reparations do not need to be a zero-sum game in which one side wins and the other side loses. That outcome would inevitably cause psychological harm for some, with benefits for others. In reparation, along with truth and reconciliation, all can win and feel better about themselves. African, Indigenous, and Asian Americans, as well as climate refugees, will contribute more to our country and the world if they are valued appropriately. The health and success of all populations is paramount to the global success of maintaining a healthy planet and reducing the damage of climate instability.

Dr Moffic is an award-winning psychiatrist who has specialized in the cultural and ethical aspects of psychiatry. He serves on the Editorial Board of Psychiatric Times™. Dr Bailey serves as assistant dean of clinical education at Charles R. Drew University of Medicine and Science in Los Angeles, California, and Chief Medical Officer at Cedren Health Systems Inc in Los Angeles. Dr McLean is a clinical professor and Chair of the Department of Psychiatry and Behavioral Science at the University of North Dakota School of Medicine and Health Sciences in Grand Forks.

Dr Okamoto is a psychiatry specialist in Santa Ana, California.

REFERENCES
20. Did you miss August 2020’s discussion on addressing racism? Take a look at where we were to compare with where we are by visiting www.psychiatrictimes.com/view/dismantle-racism-in-psychiatry-society

Table 1. Essentials of a Psychiatric Reparations History

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<thead>
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<tbody>
<tr>
<td>1</td>
<td>Assessment of wrongs done</td>
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<tr>
<td>2</td>
<td>Assessment of psychiatric repercussions over time</td>
</tr>
<tr>
<td>3</td>
<td>Assessment of who is currently being harmed by prior wrongs</td>
</tr>
<tr>
<td>4</td>
<td>Assessment of adequacy of psychiatric rehabilitation services</td>
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Table 2. The ABCs of Psychological Reparations

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<tr>
<td>A</td>
<td>Apology</td>
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<tr>
<td></td>
<td>Apologize for scapegoating the harmed group, and adequately mourn the recognized damage done.</td>
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<tr>
<td>B</td>
<td>Benefits</td>
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<tr>
<td></td>
<td>Provide just benefits for all concerned, including increased psychiatric services.</td>
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<tr>
<td>C</td>
<td>Change</td>
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<tr>
<td></td>
<td>Alter harmful attitudes and behavior of the perpetrators for the future of current children.</td>
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<tr>
<td>S</td>
<td>Study</td>
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<tr>
<td></td>
<td>Perform follow-up outcome studies whenever reparations are provided.</td>
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Dr O’Kane is a psychiatry specialist in Santa Ana, California.

More & Evidence

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READ MORE
illnesses are afoot. Yet, none of these advances or treatments can be meaningfully implemented without a thorough history-taking, an understanding of the patient’s environment and family dynamics, and an assessment of their insight into symptoms and their willingness to engage in treatment. Most importantly, none can be implemented without the trust and connectedness that occur in a healthy patient-physician relationship.

The Art of Medical Conversation

The art of psychiatry goes back to the patient-physician relationship, the basic building block of medicine, as it has been for millennia. That relationship has evolved, of course, reflecting changes in our understanding of disease, wellness, and the roles of patients and physicians. Over the centuries, the physician has been transformed from a healer with quasi-magical powers to a partner in wellness and recovery. This evolution has been obvious through history, but only recently has scientific attention turned to what, exactly, physicians are doing that is so impactful.

In his seminal 1932 work, *The Doctor, His Patient, and the Illness*, Michael Balint, MD, PhD, coined the concept of the doctor as drug. He highlighted the importance of therapeutic interaction, calling it vital to treatment while acknowledging that the dose of this treatment—the required number of visits and the duration of visits—was not clear. Later literature developed new terminology. Mainstream medicine labeled it the “patient-physician relationship,” whereas the psychiatric field would call it nongeneric factors. Regardless of terminology, it is the *je ne sais quoi* that takes place in the intimacy of a real conversation between human beings.

What Happens When We Lose Touch

Up to 40% of deaths are attributable to modifiable behavioral factors (such as healthy eating, substance use, and physical activity).1,2 Whether or not patients modify these behaviors depends to a great extent on the level of trust they give to their physicians.3 Qualities such as availability, benevolence, compassion, competence, honesty, integrity, knowledge, reliability, respectfulness, sincerity, and understanding are cited as essential in fostering and maintaining a healthy patient-physician relationship.4 The realities of modern health care, however, are not matched to this paradigm of relationship growth, nor do they protect it. In recent decades, the foundations of clinical medicine/psychiatry have been under attack from the health care system itself. Visit lengths have sharply declined, as has the number of psychiatrists providing therapy.5 So the question must be raised: In a visit of 10 to 15 minutes, how much of a therapeutic alliance can actually be built? I fear our self-conception is changing, too. Words like *provider, prescriber,* and *mental health specialist* do not capture the centrality of the patient-physician relationship. We are at risk of losing the sense that, in the words of Hugh Crichton-Miller, MD, “[the patient] is not simply an object but a person, needing enlightenment and reassurance.”6

The health care system has been attempting to standardize aspects of the patient-physician relationship that could promote success. Bias and countertransference are 2 aspects that have been studied in context of patient encounters,7-12 and it is recognized that concordance in the patient-physician relationship is a desirable asset for successful treatment alliances.13,14 Achieving that concordance in short, sparse clinical visits may not be achievable, but the operationalization of these concepts nevertheless leads to a better understanding of nonspecific factors in the patient-physician relationship.

When physicians and patients are unable to build strong relationships, patients fare worse. In the treatment of depression, the number of meetings with the therapist or physician, regardless of the therapeutic modality, affects outcomes, even when patients are being treated with psychoactive agents.15 The working alliance becomes even more important when addressing difficult issues of trauma and addiction.16 Recent advances inform us that nonspecific factors in treatment can be conceptualized in 2 areas: expectancy and alliance. These can be further subdivided into trait-like and state-like dimensions, each with their own neurobiological underpinnings.17 Trait-like components refer to attachment and personality styles, and they influence the relationship between the patient and the individual treating them in a nonspecific manner.18 When used optimally and at the right time, state-like dimensions can be used as active ingredients for change in therapy. Technological advances allow us to study the therapeutic alliance as it evolves session by session, taking into account within-person fluctuations and stable between-person differences.19

The therapeutic alliance is also crucial to overcoming mental health stigma. Individuals sometimes resist psychiatric labels, and some patients may be harassed for using mental health care. To bridge that gap, we resort to the art of psychiatry, the alliance in the patient-physician relationship that helps patients see their treatment as a means to achieve life goals and recovery.

Concluding Thoughts

The patient-physician relationship is what the upcoming *Psychiatric Times* series, *Tales of The Clinic: The Art of Psychiatry*, is all about. The cases discussed are fictional, but they represent common presentations. Moving from the case, the human story, we transition to the evidence-based application of psychiatric research, highlighting the complex interplay of art and science. As readers will note, some of the cases span years of treatment. Many patients will say that they never thought their improvements were possible, and that treatment has given them a new life. But progress is not possible without both art and science—the art of human rapport, and the science that brings us effective, precise treatments.

So, to all my fellow psychiatrists and therapists, this is a love letter to our wonderful field, where the magic of medicine is still alive. Your comments on these cases are welcome. Please send them to PTEditor@MMHGroup.com.

Dr Moukaddam is associate professor, Menninger Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine, and Ben Taub Adult Outpatient Services director, medical director, Stabilization, Treatment & Rehabilitation (STAR) Program for Psychosis. She also serves on the Psychiatric Times® Advisory Board.

REFERENCES

TALES FROM THE CLINIC

I Had to Use

» Roberto D. Sanchez, DO; Benjamin Li, MD; and Nidal Mokkadd MD PhD

In this installment of Tales From the Clinic: The Art of Psychiatry, we cover an intriguing case of dual substance use super-imposed on mood, anxiety, and trauma clinical picture. A significant challenge for this group of patients is the need for patient, methodical, consistent care to unravel the complex multifaceted triggers and perpetuating factors for continued maladaptive behaviors. The case description spans years of treatment and, while the details may seem sensational, they reflect the reality of what the addiction treatment clinic team encounters. In addition, there is much difficulty in hearing and processing patient accounts of trauma, which could lead to physician burnout.

CASE VIGNETTE

“Ms Martin” is a 45-year-old female with bipolar disorder, generalized anxiety disorder, and suspected borderline personality disorder. She was transferred to the substance use disorders clinic by another psychiatrist after a diagnosis of opioid use disorder was obvious. At the time of her transfer, she was involved in prostitution to finance her roughly 25 tablets of acetaminophen and hydrocodone daily. Her opioid use disorder history had a protracted course, with her first exposure to prescription opioids at the age of 16 following a significant injury requiring surgical intervention. Her longest lifetime period of sobriety was 2 years.

Her immediate environment was not conducive to recovery, as she lived in a trailer with a male roommate who had mutual acquaintances that provided pain pills. In addition, Ms Martin engaged in sexual activity with the roommate in exchange for opioids. As time progressed, the relationship became physically abusive; she left after her roommate tried to hit her with a vacuum cleaner when she “didn’t do a good job cleaning the trailer.” At the time, she had been in treatment for 1 year, was started in medication-assisted therapy (MAT), and had been prescribed buprenorphine. She moved into an apartment with her mother, which greatly reduced access to opioids. She was not fully aware of what she was taking, but she thought it might have been amphetamine since it came in a “large jar with many capsules.” Testing verified the presence of methamphetamine.

Three years into treatment, Ms Martin met a new boyfriend. Her urine drug screen (UDS) resulted positive for amphetamine. He provided her with substances that boosted her energy and aided in weight loss. She was not fully aware of what she was taking, but she thought it might have been amphetamine since it came in a “large jar with many capsules.” Testing verified the presence of methamphetamine.

These results were shared with Ms Martin, to her genuine surprise, and she expressed earnest motivation to stop methamphetamine use. Unfortunately, over the next year, she eventually met criteria for stimulant (methamphetamine) use disorder. This paralleled toxic developments in her relationship. She described a continued strong sexual attachment to her partner, and she remained intimate with him despite knowledge that he was simultaneously sexually active with her mother. She later bashfully admitted engaging in group intercourse with her partner and mother. During intercourse she described her partner’s derogatory and sadistic tendencies, which she felt she “deserved.”

Eventually, she developed disgust toward him. This resulted in an internal conflict because while she described feeling revolting by him, she simultaneously experienced severe loneliness and feelings of abandonment when he did not give her attention. This fueled further methamphetamine use as she wanted to be “skinny and pretty.”

The ongoing sexual relationship between her partner and mother resulted in significant tension within the apartment they all shared. On multiple occasions, Ms Martin described anxiety that her partner and mother were colluding against her. Methamphetamine use may have intensified these feelings. Although at times she expressed a desire to leave, she felt she had nowhere to go. Her partner contributed to paying bills, which further complicated her situation. For the next year, Ms Martin continued to express significant ambivalence about her relationship. She recognized how the situation placed a strain on her relationship with her mother, yet she simultaneously feared the rejection, abandonment, and loneliness that would result from a breakup. She described symptoms of anxiety and sadness when away from her partner, and he was using methamphetamine pills as a tool to control her. She compared her “love-hate” relationship with her significant other with that of her relationship with the methamphetamine pills.

In addition to work in building Ms Martin’s feelings of self-worth and autonomy, a motivational interviewing style was utilized to help her resolve some of her ambivalence toward the relationship. Although she voiced much more change talk to end the relationship, compared to sustain talk, she had difficulty committing to ending the relationship.

Pharmacological Considerations

Due to the alarming rate of opioid overdoses secondary to fentanyl, clinicians and those struggling with substance use are becoming aware that the product purchased is not always marketed. Anecdotal reports of increasing concomitant opioid and amphetamine use abound, but the condition is not well understood, nor systematically studied. In the case of this patient, confirmatory test showed methamphetamine, whereas she believed she was getting amphetamine or methylphenidate; she may have inadvertently gained access to a supply of methamphetamine.

Currently, there are no US Food and Drug Administration-approved treatments for methamphetamine use disorder. Some studies suggest the use of bupropion, naltrexone, and mirtazapine may have some limited efficacy in specific populations.1-3 In addition to treating Ms Martin’s SUD, the team addressed co-occurring mood and anxiety symptoms (she had witnessed her brother injured in a car accident). Her initial regimen included duloxetine and aripiprazole for depression, anxiety, and mood stabilization. Bupropion was not tried due to her concern of its risk of exacerbating her anxiety, and she declined mirtazapine due to its risk of weight gain because she already struggled with her body image. After Ms Martin expressed concerns...
that aripiprazole may be contributing to her weight gain, she was switched to cariprazine. With continued work, despite ongoing personal conflict, financial instability, and continued methamphetamine use, Ms Martin increased engagement in treatment and is adherent with all medication management visits. The treatment team ultimately decided not to taper off the buprenorphine, given her gradual progress toward treatment goals was a product of a harm-reduction approach. She could have benefited from inpatient rehabilitation. However, reluctance to go into rehabilitation is common in patients with SUD. Additionally, drug use is perpetuated by perceived benefits, and cessation of use does not happen unless the patient appreciates the negative impact of substance use on their lives. When Ms Martin finally understood she was taking methamphetamine, it created an opportunity to see its use as a problem instead of an agent for cognitive enhancement/weight loss. Methamphetamine is commonly used to improve sexual function. In fact, the literature has described methamphetamine as increasing sexual desire, pleasure, reducing the refractory period between intercourse, exacerbating impulsiveness, and impacting behavioral inhibition.4,5 In this case, it would be worth further exploring that idea, as the patient’s partner was supplying methamphetamine and requesting particular sexual demands. A major challenge in the field continues to be the lack of available effective pharmacologic treatments for stimulant use disorders. Contingency management in combination with community reinforcement is a proven effective behavioral treatment for stimulant use disorders, as confirmed by multiple meta-analyses.5 However, there are considerable barriers to implementing contingency management at this time, including public stigma and ongoing struggles with stimulant use, patients demonstrating resilience and often continue to express desire for full recovery. Cognitive-behavioral therapy, relapse prevention, mindfulness, and psychodynamic therapies are all useful in treatment, but the level of complexity of patients with SUD often means a prolonged course of treatment with multiple modalities needed.

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Psychiatry is associated with the brain, but there is so much more to it than that. We are the field within medicine that deals with humanity. As such, we can be the field that serves as a conduit toward dismantling racial and social injustices in health care. Indeed, psychiatrists are equipped with the tools to engage in a healthy discourse when discussing topics that may have a proclivity toward inspiring defensiveness and fragility. And we recognize that when there is division in the body, all parts suffer.

What our field does today regarding the topics of diversity, equity, and inclusion will reverberate throughout the walls of the inpatient wards, residency/fellowship programs, ambulatory clinics, and community mental health centers for centuries to come. I embolden us to practice humility and to cultivate a growth mindset that diverges from the status quo. Answering the call of these exhortations is vital if the health care disparity gap is be narrowed.

With that in mind, I hope that this 2-part series will help improve our cognitive flexibility and our ability to rethink how we provide care for our patients using the bio-psycho-social-cultural-spiritual model. Over these Special Reports, we aim to share insights and tips to support you in providing meaningful care to those from minority populations and backgrounds.

Dr Clark is clinical assistant professor at the University of South Carolina School of Medicine -Greenville and medical director and division chief for Adult Inpatient and Consult-Liaison Services for the Department of Psychiatry and Behavioral Medicine at Prisma Health - Upstate. He served on the American Psychiatric Association’s Task Force to Address Structural Racism Throughout Psychiatry, and he currently serves as the Diversity and Inclusion section editor and advisory board member for Psychiatric Times™.

I leave you with some food for thought in the form of this haiku:

Courage to conquer and deliquesce division shines humanity
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There is no evidence that doses greater than 60 mg/day confers additional benefit, while some adverse reactions were observed to be dose-dependent

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Asian American Mental Health: Treating a Diverse Population at a Crossroads

Geoffrey Z. Liu, MD; Margaret Cheng Tuttle, MD

REPORT

REPREHENSIBLE REgressed SENTIMENTS
First Yellow Peril
Now model minority
Back to viral slum - FRANK CLARK, MD

The shocking Atlanta mass shooting in March 2021 that resulted in the deaths of 6 Asian American women brought the nation’s attention to the rise in anti-Asian violence since the advent of the COVID-19 pandemic. The increase in hate speech, property damage, and brutal attacks, coupled with the negative mental health impact of quarantine isolation, has led to an increase in feelings of anxiety and distress among Asian Americans.1,2 With this confluence of stressors, we anticipate more Asian Americans will present for psychiatric care. Given the shortage of psychiatrists with expertise in working with Asian American patients,3 it seems timely for us to share some insights on both acute and longer-term issues facing Asian Americans.

Before we begin, a caveat: Asian Americans are an incredibly diverse group, representing more than 20 countries of origin and hundreds of languages and cultures. The needs of immigrants differ from those of American-born Asians. There are wide differences in socioeconomic status, insurance status, educational background, age, and degree of acculturation. Although case presentations are inadequate to capture the diversity of this population, the cases are used to illustrate some of the issues with enhanced nuance and depth.

Case 1

“Ms Cho” is a 37-year-old married professional Korean American woman with a history of major depressive disorder (MDD) and generalized anxiety disorder (GAD). Although she has been on a long-term stable dose of sertraline, her mood and anxiety have gradually worsened in recent months, and she reports feeling inexplicably “overwhelmed.” She finds herself struggling to keep up with work demands. Her psychiatrist, “Dr Williams,” who is not Asian, asks if this feeling has anything to do with the recent rise of anti-Asian violence. Ms Cho thinks for a moment, then nods. She discloses that she is constantly worried about the physical safety of her parents and her 2 school-aged children. She is also having intense memories of being bullied when she was in grade school. She finds herself thinking about these incidents, now with an adult’s perspective, and realizing the long-term impact these incidents have had on her life.

Anti-Asian racism in the United States began with the arrival of the first Asian immigrants in the 1850s. Frequently seen by Whites as “uncivilized, unclean, filthy beyond all conception,” Asians were labeled the “Yellow Peril” and “perpetual foreigners.” Over the subsequent 75 years, legislation such as the Exclusion Act (1882), Immigration Act (1917), and Johnson-Reed Act (1924) was passed to severely restrict immigration from Asian countries and to make those who did immigrate ineligible for citizenship. In 1965, the United States relaxed immigration restrictions from Asia, and a second wave of more affluent, highly skilled Asians immigrated to this country. Perception of Asian Americans shifted from revulsion to admiration, as Asian Americans attained educational and professional success. Asian Americans came to be known as a model minority, with success attributed to aspects of Asian culture, as compared with that of other ethnic minorities.

The recent rise in anti-Asian attacks reveals the fragility of the model minority myth. In the wake of COVID-19, Asians are no longer seen as educated hard workers worthy of admiration, but instead as carriers of disease, harrowing back to the first racist insults. Furthermore, the attacks, which often take place in broad daylight with bystanders around, leave many Asian Americans feeling vulnerable and needing to be vigilant. One Asian American author eloquently describes the feeling of vulnerability: “I’m seen for my race above anything else,” she said. “I can be a Brown University student or a professor, but if I walk out onto the street, I will first and foremost be seen as an Asian and could still be attacked for that.”9

There has been a recent recognition that the strife associated with racism can rise to the level of traumatic stress,4,5 which can cause symptoms characteristic of posttraumatic stress disorder (PTSD): intrusive thoughts and memories, anxiety, and feelings of being unsafe, as experienced by Ms Cho. Thus, we could consider Ms Cho’s current symptoms to be products of vicarious trauma, triggered memories of earlier childhood racial trauma. While Ms Cho’s symptoms may not rise to the threshold level of PTSD (Dr Williams would need to perform a more comprehensive evaluation to say so definitively), subthreshold traumatic stress symptoms can exacerbate preexisting comorbid conditions, such as MDD and GAD.

While no empirically validated treatment models exist yet for managing symptoms associated with ethnoracial trauma, experts do recommend a few ground rules (Table 1).

In addition to the above general principles, consider some of the interventions described in Table 2.

Case 2

“Mr Sok” is a 58-year-old Cambodian American man referred by his primary care doctor to psychiatrist “Dr Smith” for chest pain with unremarkable cardiac workup. Because the clinic is without a Khmer translator, Dr Smith asks the accompanying daughter to provide translation.

The patient describes that he is worried that his chest pain could mean that he is developing, in his words, a “weak heart.” He also worries about tension in his body, which he takes to be a sign that his body is “falling apart.” Dr Smith, believing Mr Sok to be suffering from somatic symptom disorder, prescribes escitalopram. She explains the neurobiology of anxiety disorders; she notes the medication will help with his anxiety and suggests he return in several weeks. Mr Sok looks visibly puzzled but agrees to the treatment plan. Mr Sok does not fill the medication and is lost to follow-up.

Many Asian American immigrants have spent more time outside of the United States than in it. Consequently, a patient’s experience of their illness—their beliefs about its cause, its treatment, its meaning—is likely influenced by their culture of origin and by Western concepts like psychiatric diagnosis. Clinicians would do well to mind the gap between the psychiatric explanation and their patient’s. Ignoring this gap can lead to problems such as misdiagnosis, medication nonadherence, or early treatment rupture, as in Mr Sok’s case.

We recommend explicitly soliciting the patient’s cultural understanding of their illness using

Table 1. Ground Rules for Managing Symptoms of Ethnoracial Trauma

1. Be aware of how your race may be perceived by your patient. If a patient has experienced racial trauma perpetrated by members of the psychiatrist’s racial group, it may impede disclosure of racial trauma to the psychiatrist. Naming that difference early on in treatment can be helpful, eg, “Patients and psychiatrists can differ in ways such as their age, gender, and race. Please let me know if you have any thoughts or feelings that come up about our differences.”

2. Name racism as a factor if symptoms suddenly worsen. Taking a cue from Dr Williams, asking Ms Cho directly about the impact of racism on her symptoms signals to her that this is a safe subject to discuss and lays the groundwork for trust between psychiatrist and patient around issues of race.

3. Do not make things worse. When a patient discloses their experience of racial trauma, this is a high-stakes moment. Do not ignore the disclosure. Do not deny the impact. These responses are likely to enhance shame around the experience and entrench avoidance of the experience. It also robs the patient of the ability to gain some measure of control over the incident through disclosure.
MINORITY MENTAL HEALTH

Table 2. Interventions to Suggest That May Help Patients With Ethnoracial Trauma

- Limit exposure to social media and news
- Limit interaction with individuals or situations that feel psychologically or physically unsafe
- Individual psychotherapy focused on understanding the patient's experience
- Holistic modalities such as acupuncture, Reiki, or craniosacral therapy; these may be especially helpful as they could feel culturally concordant
- Avoid isolation in the face of trauma by sharing stories with family, friends, support network, and community
- If so inclined, channel feelings into advocacy and understanding the causes of racial hostility in our country
- Learn techniques for responding to microaggressions such as “Interrupt, Question, Educate, Echo”10

- INTERRUPT: “Just a second—let’s get into your point that the virus is somebody’s fault.”
- QUESTION: “Why do you think that?”
- EDUCATE: The key to educating is to continue the conversation.
- ECHO: It takes an effort to speak up against racist ideas and language. When someone else speaks up, echo them. Thank them and emphasize or amplify their message any way you can.

Many Asian-born Americans struggle navigating 2 cultures: They strive for acceptance from the host culture on the one hand, and they strive for acceptance from their family and the culture of origin on the other. This added conflict can complicate the already onerous process of identity formation in adolescence, setting the groundwork for psychiatric symptoms and problematic behaviors.

Furthermore, Asian American immigrant parents tend to judge their child’s behavior and actions by the cultural standards of the country of origin and are apt to make suggestions that may miss the bicultural nature of the conflict. For example, Mrs. Chen’s suggestion to minimize socializing and focus on schoolwork may be well-received by a student who grew up in China, but to Elizabeth, this suggestion is likely to feel invalidating of her desire to acculturate, fueling further frustrations that her mother does not understand.

What can a treating psychiatrist do to help the situation? In addition to recommending standard behavioral treatments for problematic behaviors such as cutting, Dr. Santos might also suggest a family intervention, using the Bicultural Effectiveness Training framework as an approach.11,12 Specifically, Dr. Santos could gently reframe the problem as a conflict of cultural perspectives rather than a conflict of individual personalities and reflect with both parent and child on the advantages and disadvantages of each cultural perspective. For example, Dr. Santos might ask Elizabeth and Mrs. Chen to reflect on situations when spending less time with friends might be a good solution to stress and when it might not be a good solution.

Elizabeth’s case also illustrates the damaging effects of the model minority stereotype on the individual. Asian Americans like Elizabeth can feel immense pressure to live up to an image of success, exacerbating academic stress and leading to concealment of mental health symptoms. Of all US racial groups, Asian Americans are the least likely to seek mental health care, and while the reasons for this inequity are complex, the perpetuation of the model minority myth likely contributes to this disparity.16,17

Conclusions
By presenting these 3 cases with patients of varying ages, national origins, language proficiencies, and presenting problems, we hoped to capture a fragment of the diversity and showcase some of the main issues facing this population. The techniques highlighted might be helpful not only for Asian American patients, but across cultures as well. In fact, we might think about these techniques as ways for clinicians to assume a general attitude of cultural humility—a position of openness, self-awareness, and curiosity—that is useful in all encounters with patients, regardless of race or cultural background (Table 3).14

We hope that some of the strategies in this article may help in that effort to treat Asian American patients. However, when it comes to treating symptoms that are produced by systemic forces like racism and alienation from mainstream American culture, bearing witness to a patient’s experience of racism is like treating the symptoms without addressing the underlying cause. A truly comprehensive treatment plan for Asian American patients.

Table 3. Culture and Problem-Solving

<table>
<thead>
<tr>
<th>CULTURAL DEFINITION OF THE PROBLEM</th>
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<tbody>
<tr>
<td>1. What brings you here today?</td>
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<tr>
<td>2. How would you describe your problem to family and friends?</td>
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<tr>
<td>3. What troubles you most about your problem?</td>
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<table>
<thead>
<tr>
<th>CULTURAL PERCEPTIONS OF CAUSE, CONTEXT, SUPPORT</th>
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<tr>
<td>4. Why do you think this is happening? What do you think is causing it?</td>
</tr>
<tr>
<td>5. What do your family and friends think is causing it?</td>
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<tr>
<td>6. Are there any kinds of supports that make your problem better?</td>
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<tr>
<td>7. Are there any kinds of stresses that make your problem worse?</td>
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<table>
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<tr>
<th>ROLE OF CULTURAL IDENTITY AND SELF-COPING</th>
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<tr>
<td>8. For you, what are the important aspects of your background or identity?</td>
</tr>
<tr>
<td>9. Are there any aspects of your background or identity that make a difference to your problem?</td>
</tr>
<tr>
<td>10. Are there any aspects of your background or identity that are causing other concerns or difficulties for you?</td>
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<tr>
<td>11. What are some of the things you have done on your own to cope with your problem?</td>
</tr>
<tr>
<td>12. In the past, what kinds of treatment, help, advice, or healing have you sought for your problem?</td>
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<tr>
<td>13. Has anything prevented you from getting the help you need?</td>
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<tr>
<th>CULTURAL FACTORS AFFECTING CURRENT HELP-SEEKING</th>
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<tr>
<td>14. What kinds of help do you think would be most useful to you at this time for your problem?</td>
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<tr>
<td>15. Are there other kinds of help that other individuals have suggested to you?</td>
</tr>
<tr>
<td>16. Do you have any concern that we may be misunderstanding each other because of our different backgrounds and experiences?</td>
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Adapted from Cultural Formulation Interview.10
Reconceptualizing Hispanics in America: From Reading Stark Statistics to Confronting Racial and Ethnic Trauma

Maria José Lisotto, MD; Andrés Martin, MD, MPH

According to the 2019 US Census Bureau population estimate, Hispanics comprise 18% of the total US population (61 million), with 31% aged less than 18 years, making them the nation’s largest and youngest racial and ethnic group. Since more than half of mental health disorders begin by age 14 years, and 75% by age 24 years,2 the role of culturally humble, curious, and attuned child and adolescent mental health professionals is critical. Although we will use the terms Latino/Latina, Latinx interchangeably, there are distinctions between them: “Hispanic” refers to a common language and describes those whose ancestry derives from Spain or Spanish-speaking countries; “Latinx/Latina,” most recently replaced by the gender-neutral alternative “Latinx,” refers to geography and indicates a Latin American origin.3 The federal government recognizes just 1 ethnic group in its classification system: according to the 2010 and 2020 Census, “Hispanic or Latino” and collective label- ing of several self-sustained ethnicities can lead to overgeneralizations, misconceptions, and stereotyping of the diverse Latinx community. The prevalence and clinical presentation of mental illness, the willingness to seek and accept care, and lived experiences can vary significantly among Latinx subgroups. Given this heterogeneity, clinicians should embrace such diversity, recognizing the clinical importance of providing respectful subgroup-specific care (Table 1).

Latinx individuals often face inequities in education, socioeconomic status, insurance coverage, and even risk of death related to police inter- vention. Unfortunately, disparities are further exacerbated among Hispanics due to language barriers and undocumented immigration status. Patients with limited English proficiency or En- glish as a second language struggle during mental health visits; communication of abstract concepts such as emotions and psychiatric symptoms in a language other than one’s mother tongue is extremely challenging, especially during times of internal distress.4

Stark Statistics
According to the US Census Bureau, Hispanics on average hold a lower educational level in the United States compared with other racial and ethnic groups.5 Hispanics also have the highest uninsured rates of any racial or ethnic group within the United States (19% of the Hispanic population was not covered by health insurance vs 6% of the non-Hispanic White population).6 Similarly, the unemployment rate and the percentage of individuals living at or below the pov- erty level are higher for Hispanics as compared with non-Hispanic Whites.1

Further complicating such disparities, food insecurity is associated with a heightened risk of past-year mood, anxiety, and substance use dis- orders in children.7 Poverty and mental illness interact in a negative cycle: Individuals who live in poverty are at increased risk of mental illness and, in turn, there is an increased likelihood that those living with mental illness will drift into or remain in poverty.8

Hispanics have the highest prevalence 17% of type 2 diabetes in the country8; for non-Hispanic Whites, the prevalence is 8%.9 Di- abetes is also increasingly recognized as a risk factor for serious mental illness, depression being twice as high in individuals with type 1 or type 2 diabetes compared with the general popula- tion.10 However, given the diversity within Latinx/Hispanics, it is not surprising that the rates of illness can also vary significantly within sub- groups. For example, Puerto Ricans are twice as likely as someone whose background is South American to develop type 2 diabetes;10 Puerto Ricans also suffer disproportionately from asthma, HIV-AIDS, and infant mortality.11

According to a 2019 US Census Bureau report, 24% of Hispanics, in comparison with 15% of non-Hispanic Whites, worked within service occupa- tions; 24% and 45%, respectively, worked in managerial or professional occupations.1 These differences in occupations explain in part why Latinx parents have difficulties accessing medical care for themselves and their children: Hispanics are more likely to work in jobs that do not provide paid time off; at other times, they do not request sick leave due to fear of, or threats of, deportation by employers. Communication and language barriers, cultural differences between
patients and providers, and historical and current discrimination in health care systems are other factors affecting access to health care, especially psychiatric care.

**Latinx Victims of Police Shootings**

According to data compiled by *The Washington Post*, 111 children have died by police use of force in the United States over the past 6 years; 22 of those children were aged less than 16 years, and three-quarters of these 22 were children of color.1 One of those children was Adam Toledo, a Latinx 13-year-old boy who, although unarmed, was shot and killed by police in Chicago after an officer believed the boy was holding a weapon. A recent study published in *Pediatrics* found that Black and Hispanic adolescents are significantly more likely to die from shootings related to police intervention compared with non-Hispanic White adolescents.2 Compared with non-Hispanic White children, Latinx children had a risk of death due to legal intervention almost 3 times higher. These disparities are clear and unacceptable, and they should alarm clinicians, especially those caring for children and adolescents of color.

These data are not only heartbreaking but point to inescapable effects on the mental health, physical health, well-being, and overall future of the family members left behind. The death of a young Latinx male, often the primary breadwinner for immigrant or first-generation families, leaves a void within the family system and the overall community. The offspring of the young victim grow up without a male role model, directly affecting the overall sense of safety offered by a tight-knit family. It also leads to the need for single mothers to take multiple jobs to make ends meet, causing a rupture in the family system, with older siblings often taking the role of primary caretakers for younger siblings, in turn increasing the likelihood of dropping out of high school and decreasing the likelihood of college attendance; lower levels of educational attainment limit future job options and lead to lower-paying or less stable jobs.

The alarming frequency of young Black and Hispanic individuals’ deaths by gunshot wounds during police encounters have a wide-ranging impact on the entire community, exacerbating feelings of hopelessness, oppression, discrimination, and distrust in the legal system. In our clinical experience this, in turn, can have the unwanted effect of further alienating communities of color from medical and political systems that are often viewed as complicit, leading to fewer medical check-ups, less openness to seek medical or psychiatric attention when needed, and even less likelihood to vote, further perpetuating the cycle of discrimination and isolation for generations to come. Research has shown that police violence can take a toll on the mental health of communities; police brutality and killings can be associated with greater risks of distress and suicide attempts.3

**Race and COVID-19**

The year 2020 saw 2 major cultural phenomena: the COVID-19 pandemic, and a resurgence of the conversation around racial equity and structural racism in the United States.4 The synergistic nature of the health and social problems facing people of color, as well as the toxic stress resulting from racial and social inequities and marginalized experiences during the pandemic, bringing to the forefront disparities in access to care among Latinx communities. According to data gathered through March 2021, Latinx Americans had experienced 18% of COVID-19–related deaths in people of known race.5 Latinx individuals were held in precarious and at times inhumane conditions in US Immigration and Customs Enforcement (ICE) detention facilities, and individuals in ICE facilities had rates of SARS-CoV-2 infection that were 6 to 22 times higher per month than those of the general population between April and August 2020.6 Children and families in immigration detention settings and those experiencing homelessness and living in shelters endured similarly disproportionate risk of exposure.

Latinx youth and their families have been impacted severely by COVID-19, with Centers for Disease Control and Prevention (CDC) data showing disproportionate hospitalization rates (more than 3 times higher compared with non-Latinx Whites), and death rates that are more than twice as high.7 Latinx children had higher pediatric case rates, hospitalizations, and virus-related complications.8 Poor access to reliable or sustainable tele-health technology among Latinx children worsened health care access and exacerbated gaps in educational attainment, especially throughout the multiple lockdowns and in-person school cancellations during the COVID-19 pandemic.9

Health care barriers, including lack of insurance and immigration fears, have also contributed to the worsening of pre-existing health conditions (eg, asthma, diabetes) and delays in COVID-19 treatment during acute illness and for aftercare.10 In addition, Latinx individuals, especially undocumented immigrants, have limited job options, do not have paid sick days, and often endure unhealthy work environments in which employers use threats or fear of deportation to their advantage. When they do get sick or are symptomatic, they continue working, increasing their own risk of worse outcomes from COVID-19 and potentially spreading the virus among coworkers.

Adding insult to injury, there is a large gap in COVID-19 vaccination rates for Hispanics. Black and Hispanic individuals have received a smaller share of vaccinations in proportion to the cases and deaths in their populations, and, in most states, in proportion to total population. Across 42 states, the percentage of the White population that has received at least 1 COVID-19 vaccine dose (39%) was roughly 1.5 times higher than the rate for Black (25%) and Hispanic individuals (27%) as of May 3, 2021.11

**Racial and Ethnic Trauma**

The American Academy of Pediatrics published “The Impact of Racism on Child and Adolescent Health” in August 2019. This policy statement, endorsed by both the American Academy of Child and Adolescent Psychiatry and the American Psychiatric Association, states that “racism, which is mediated through implicit and explicit biases, institutional structures, and interpersonal relationships, is a social determinant of health that underpins health equity for all children, adolescents, emerging adults, and their families.”12 The race-based traumatic stress theory suggests that some racial and ethnic minority individuals may experience racial or ethnic discrimination as a psychological trauma, as it may elicit a response comparable with posttraumatic stress.13 These experiences of racial or ethnic discrimination include threats of harm and injury, humiliating and shaming events, and witnessing harm to other people of color due to real or perceived racism.

Experiences of marginalization and discrimination have led to chronic and toxic stress, and they have shaped social and economic factors affecting the health and well-being of Latinx communities. Maladaptive reactions to racial and ethnic discrimination through use of avoidant or passive coping strategies may render minority groups, particularly youth, more vulnerable to negative mental health outcomes, including posttraumatic stress and dissociative symptoms. Flores et al found that Mexican American adolescents who reported racial discrimination also reported more posttraumatic stress symptoms, and in turn, greater drug and alcohol use—a common avoidant coping strategy.
evident in trauma-exposed individuals. Factors including a strong racial/ethnic identity, ethnicity/racial socialization within family, and religiosity/spirituality have shown to be protective against the damaging effects of racial and ethnic adversity.

Concluding Thoughts

Historical bias, lack of culturally humble and aware providers, inadequate or misinformed care, fear of deportation, language barriers, and under-representation of Latinx child psychiatrists are just a few of the factors that exacerbate disparities in access to care among Latinx communities. Clinicians should use a cultural component in their formulation when conceptualizing clinical presentations, thinking ethnographically while remaining patient-centered so that patients and families can teach providers about their own culture. Clinicians should not shy away from asking patients about experiences they have had in facing racism, discrimination, or hierarchical mistreatment. An understanding of patients’ sociocultural background, including experiences of discrimination and racial/ethnic trauma, will have important effects on treatment adherence and the likelihood of seeking future care.

We should continue working to address existing socioeconomic, health care, and structural inequities, which place so many children and families at risk of poor outcomes (Table 2). Health interventions that consider the nuances of race, ethnicity, culture, and community differences, provided by self-aware and culturally humble clinicians, have a vital role in reducing health disparities, promoting health equity, increasing trust in systems of care, and improving both the physical and mental health of Latinx children, adolescents, and families.

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COVID-19 Brings Anosmia to the Attention of Psychiatrists

Barbara Schildkraut, MD; Margo Lauterbach, MD; Lindsey MacGillivray, MD, PhD; Shreya Raj, MD

Loss of the sense of smell—anosmia—can be devastating. Without smell, patients describe feelings of emptiness, isolation, and emotional distress. Given that anosmia is a common first symptom of COVID-19 and a long-term sequela for as many as 10% of patients who have had COVID-19–related anosmia, psychiatrists need to be familiar with this symptom in order to identify and manage the associated psychological effects.

Prior to the current pandemic, anosmia and hyposmia (decreased sense of smell) received little attention in the popular press or in the non–ear, nose, and throat (ENT) medical literature. However, disturbances in the sense of smell have become a widespread focus of concern now that anosmia has emerged as a possible first symptom—and sometimes the only symptom—of infection with the SARS-CoV-2 virus.

For most individuals who have a COVID-19–related loss of smell, the deficits are short-lived. But for those individuals who do not fully recover, the neuropsychiatric consequences can be debilitating. Pleasures of eating are lost when one cannot detect the complex scents of food. Atmospheric odors disappear: the smells of the kitchen and garden, the gym, the sea. A sense of vulnerability may ensue without the ability to detect signals of danger (eg, smoke, gas, spoiled food). It is not uncommon for depression to emerge as a result.

The pandemic-related increase in the prevalence of anosmia has thrown its debilitating effects on mood and quality of life into sharp relief and presents an opportunity for psychiatrists to help.

A Brief History Lesson

The SARS-CoV-2 virus was first reported in December 2019, although the association between anosmia and this viral infection initially was not made. Then, in late March 2020, Hopkins and Kumar sent a bulletin to Public Health England, noting high rates of COVID-19 infection “amongst ENT surgeons compared [with] other health care workers.” They reported that physicians and surgeons from around the world had noticed a significant increase in the number of otherwise asymptomatic individuals who were presenting with an abrupt onset of anosmia. They hypothesized that these patients could be unsuspected carriers of the SARS-CoV-2 virus and advised the use of full personal protective equipment for clinicians examining any patient with anosmia.

During this early stage of the pandemic, individuals across the globe did not qualify for COVID-19 testing if their only symptom was anosmia; however, in countries where COVID-19 testing was widespread, patients who tested positive for COVID-19 often had anosmia, and frequently anosmia was their first symptom. By April 2020, the Centers for Disease Control and Prevention had added sudden loss of smell and/or taste to the diagnostic criteria for COVID-19.

Pathophysiology

Researchers have considered various pathophysiological theories to explain COVID-19 anosmia. The most plausible explanation is viral infiltration of support cells of the olfactory epithelium (sustentacular cells), inflammation, and subsequent neuronal dysfunction.

The sustentacular cells of the olfactory epithelium are especially vulnerable to viral damage due to having a high density of ACE2 cell surface receptors. The ACE2 receptor is a known entry point for the COVID-19 virus.

For individuals with a protracted course of anosmia, the pathway to regaining olfaction may be marked by experiences of unpleasant, distorted, and often repugnant smells (parosmia). In some cases, individuals may have hallucinatory smells (phantosmias). The mechanisms that underlie these phenomena are still unclear but may be related to imbalanced rewiring of regenerating olfactory neurons or immaturity of neuronal networks when stem cells have been recruited to replace damaged olfactory neurons.

Smell and Taste

Sensory experiences of temperature, touch, pressure, and pain (spiciness) (Table 1). The experience of taste also includes sensations from odors that are presented through the nostrils and/or via the nasopharynx.

The Etiologies

Before the current pandemic, about 3% of the adult population aged 40 years or older and up to 22% of adults aged more than 60 years were afflicted with smell disturbances. Patients with neurodegenerative diseases such as Alzheimer disease, Parkinson disease, and dementia with Lewy bodies exhibit a gradual loss of the sense of smell; often these individuals are only minimally aware of their deficit. The abrupt loss of a sense of smell can occur with head trauma or with any of numerous viral infections, including infection with SARS-CoV-2 (Table 2).

Psychological Experiences

When there is a sudden loss of the ability to smell, patients are startled by how important scents are to their daily life experience. This sudden alteration in one’s experience of the environment is unsettling and often deeply emotionally distressing.

Smell involves the basic sensations of sweet, sour, salty, bitter, and umami in addition to the somatosensory experience of temperature, touch, pressure, and pain (spiciness). Since the pandemic, newspapers and magazines have published essays by individuals who have personally
experienced COVID-19 anosmia and parosmia. The authors widely report a loss of pleasure in eating. For example: “It was first apparent that something was wrong when I took a bite of a falafel sandwich that morning and it hung like tasteless cardboard in my mouth.” These writers also comment on changes in weight and disruption to patterns of social engagement that center around sharing a meal.

Some of the articles focused on individuals who depended on the sense of smell for work: chefs, fire-fighters, and perfumers. Sommeliers commented on their experiences in Wine Spectator: “It was absolute terror. The thought of no longer being able to do so much of my job was just terrifying. And then there’s everything else in your life. I love to cook, I love more than just wine, and all of that would be gone.”

The loss of smell sensations also affected individuals in ways that are difficult to define: “I feel alien from myself... It’s also kind of a loneliness in the world. Like a part of me is missing, as I can no longer smell and experience the emotions of everyday basic living.” And this: “I feel discombobulated—like I don’t exist. I can’t smell my house and feel at home. I can’t smell fresh air or grass when I go out. I can’t smell the rain.”

In Comprehensive Psychiatry, Stefano Pallanti, MD, PhD, reported 2 cases of COVID-19–related anosmia. He quotes a patient as saying, “This strange, empty feeling makes me feel weird about my body.” The other patient was aware of feeling “distant from the world, without atmospheric cues deriving from environmental triggers.”

Although smell is arguably the least appreciated of our senses, it is extraordinarily fundamental. The sense of smell is neurologically and, therefore, experientially involved in memory formation, emotional processing, and social behavior. Smelling is inextricably intertwined with breathing, just as tasting is inextricably intertwined with swallowing. Smell is a source of extraordinarily complex, often nonconscious, information about our environment, including our social environment. We smell our babies; we smell our partners; we know the smell of our own bodies. Intimate relationships may be disrupted by disturbances in the sense of smell.

Oliver Sacks, MD, quoted a patient who lost his sense of smell. Although it followed a traumatic brain injury (TBI), the description could apply to post–COVID-19 anosmia:

**Sense of smell...? I never gave it a thought... But when I lost it— it was like being struck blind. Life lost a lot of its savour— one doesn’t realize how much “savour” is smell. You smell people, you smell books, you smell the city, you smell spring— maybe not consciously, but as a rich unconscious background to everything else. My whole world was suddenly radically poorer.**

Over time, as neurological functioning returns to normal, some individuals may experience distorted sensations of odors (parosmia) or hallucinatory smells (phantosmias). Often these sensations are repellent and can cause considerable distress, as in these examples:

**However, the most unbearable is tap water. Showering, rinsing dishes, brushing my teeth, washing my face, and many more daily encounters are now repulsive and unbearable. Living in a world where tap water smells putrid has been one of the hardest things I’ve ever gone through.**

My sweat acquired an acrid rotting-veggie–like fetid smell— swamp-like, but acidic and sharp.

### Myths
- **Acidic and sharp.**
- **Rotting-veggie–like fetid smell—swamp-like.**

### Treatments and Resources

**Of paramount importance is the psychiatrist’s role in listening to patients, gaining an understanding of anosmia’s effects on their quality of life. While anosmia may be an acute or chronic condition, in either case, managing related health problems and maximizing quality of life are key goals of treatment.**

In addressing the patient’s health problems, psychiatrists should first clarify the anosmia etiology, then identify and treat any comorbid psychiatric conditions, such as anxiety and depression. Anosmia may exacerbate an already existing mental health disorder. It is also important to determine whether a patient has been able to maintain good nutrition, hydration, and stable weight. Other health-related issues relate to personal hygiene and guarding against breath and body odor—with important social implications. Changes in relationships and intimacy can result from anosmia because of the complex relationship linking scents and social bonding. While a lack of awareness of one’s body odor can lead to poor hygiene and interfere with personal relationships, an inability to detect a partner’s scent can also negatively influence a feeling of attraction.

Like our senses of vision and hearing, our sense of smell serves not only to bring pleasure from pleasant smells and taste, but also to protect us from danger. Anosmia can make one unaware of the presence of dangerous inhalants like smoke, natural gas, and harsh cleaning ingredients. Spoiled food can go undetected, be consumed, and lead to illness. Thus, part of counseling an individual about the management of anosmia should also include advice about prevention of injury and illness. Recommendations may include installing smoke and natural gas detectors, regular maintenance to gas appliances, and dating food when opened to anticipate spoilage. Also, asking others to smell for noxious odors of any kind can be helpful.

Psychiatrists might wish to refer patients for consultation for help in managing the consequences of anosmia. If an individual’s occupation is at risk due to loss of ability to detect scents, career counseling may be useful. Individual, couples, or family therapy might be helpful, with an emphasis on education regarding anosmia and its effect on close relationships.

Smell training is the one treatment approach that directly addresses anosmia. Smell training aims to enhance the natural process of recovery by a program of consistently sniffing and concentrating on a small sample of scents multiple times a day over a period of months. The scents may be purchased as a kit, or a set of samples can be homemade.

Referrals to otolaryngologists who specialize in anosmia may be appropriate, especially for those with severe symptoms, or if there is uncertainty about the underlying cause. Many hospital-based otolaryngology departments have clinics that specialize in patient care for disturbances of smell, some of which offer smell training.

The Global Consortium for Chemosensory Research was founded in response to the outbreak of COVID-19–related anosmia. Its website has become a hub for researchers and is an easy way for patients who are interested to participate in research.

Other resources include the book *Navigating Smell and Taste Disorders*, which was published in 2010 as part of the Neurology Now book series. Although it was written before the current pandemic, this book is nonetheless useful for individuals with COVID–19–related disturbances in smell and taste. Written for a general audience, it includes numerous recipes that were developed to emphasize aspects of the food experience to enhance the pleasure of eating for those with disturbances in the experience of taste. Nutritionists also may be able to advise patients on how to modify food preparation and seasoning to emphasize aspects of taste that do not rely on smell.

Several websites by nonprofit organizations offer support to those suffering with anosmia.

### Table 2. Some Causes of Anosmia/Hyposmia

<table>
<thead>
<tr>
<th>Cause</th>
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<tr>
<td>Infection with SARS-CoV-2, even without rhinorrhea</td>
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<tr>
<td>Other viral upper respiratory infections (eg, rhinovirus, parainfluenza, Epstein-Barr virus, other coronavirus infections)</td>
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<tr>
<td>Sinus/nasal disease</td>
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<tr>
<td>Traumatic brain injury</td>
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<tr>
<td>Exposure to toxins/drugs</td>
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<tr>
<td>Neurodegenerative diseases (eg, Alzheimer disease, Parkinson disease)</td>
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<tr>
<td>Normal aging</td>
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<td>Congenital disorders (eg, Kallmann syndrome)</td>
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### Table 3. Possible Psychological Consequences of Anosmia

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<th>Consequence</th>
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<tr>
<td>Diminished enjoyment of food</td>
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<tr>
<td>Diminished interest in eating; disruption in food pacing; weight changes</td>
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<tr>
<td>Occupational difficulties for firefighters, chefs, sommeliers, perfumers, nurses, etc.</td>
</tr>
<tr>
<td>Concern about personal hygiene, body odor, and breath</td>
</tr>
<tr>
<td>Feeling vulnerable to food spoilage, gas leaks, fire</td>
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<tr>
<td>Disruption of social relationships</td>
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<tr>
<td>Decreased interest in sex</td>
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<tr>
<td>Decreased pleasure in and diminished information about the environment</td>
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<tr>
<td>Depression</td>
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Dr Schildkraut is an assistant professor of psychiatry at Harvard Medical School in the Department of Psychiatry at Brigham and Women’s Hospital; she is the author of several books and a blog. Dr Lauterbach is an adjunct assistant professor at the University of Maryland School of Medicine and is the director of the Concussion Clinic at Sheppard Pratt.

Dr MacGillivray is an assistant professor at the University of Toronto and a staff psychiatrist at the University Health Network. Dr Raj is a neuro-psychiatrist in Wellesley, Massachusetts; she also serves on the Harvard Medical School faculty and on staff at Brigham and Women’s Hospital.

From the Editor

Cannabis should not be prescribed by medical practitioners. However, as molecular components of cannabis are developed and garner FDA approval, those components should be prescribed appropriately.

9 Pharmacological exploration and development of cannabis components that demonstrate medical benefits should be continued. CBD is a successful model of such.

Medical practitioners should discuss cannabis with their patients only after they have attained competence in understanding the science and factual risks and benefits of cannabis components. Similar to how a practitioner would discuss alcohol or tobacco use.

With this structure in place, we have the ability to inform and support our patients appropriately. And, with more information, we can help end the cannabis confusion.

REFERENCES
Rethink Classifieds with Psychiatric Times™

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Child Abuse Allegations: Sorting Out Lies Versus Truths

Alan D. Blotcky, PhD

About half of marriages end in divorce, and approximately 6 out of 10 divorces involve children. Even when amicable, a divorce is a difficult situation. However, divorces can be tumultuous, and children often pay the price. One way this is manifested is in false allegations of abuse in child custody cases. Typically, one parent accuses the other parent of physical and/or sexual abuse of their child to gain leverage in their court proceeding. This tactic can be particularly impactful because judges tend to award primary physical custody to the parent who made the allegation, even if the accused parent’s actions are not substantiated. Thus, false allegations can be a powerful weapon to limit or deny custody and/or visitation in a vindictive manner.

Although a strong visceral reaction to an abuse allegation is expected, it can be counterproductive. Similarly, a rushed response can make the situation worse. In contrast, a wait-and-see attitude leaves the door open for a thorough evaluation before a disposition is decided upon.

To be clear: False allegations of abuse are a form of parental alienation. Alienation involves the concerted effort of one parent to undermine the other parent’s relationship with their child. Nothing could be worse than a custody decision that is based on a false allegation. To make matters worse, once a custody decision has been issued, modification of it is burdensome and an uphill challenge.

The clinical evaluation is an important part of proceedings in which allegations have been made. A successful case requires coordinated efforts among the judge, attorneys, and a court-appointed evaluator, who is often a psychiatrist or clinical psychologist.

Principles of the Evaluation

The approach outlined in this article is based on years of experience with hundreds of cases of abuse allegations, and it consists of sequential steps. The evaluation process is aimed at determining if an allegation of abuse has occurred or not—in other words, whether the allegation has been fabricated by a parent with the intent of sabotaging and harming the other parent.

For obvious reasons, the evaluation must include both parents and the child to understand the entire narrative. All 3 individuals—the accused parent, the accusing parent, and the child—must be a part of the evaluation process. After all, we want our conclusions and recommendations to be based on full and accurate information.

The accused parent is often advised by their attorney not to participate in the evaluation process. This is ill-conceived advice. By doing so, the mental health professional evaluator will be deprived of critical information that can shine a light on the falsity of the claim. Otherwise, all the information will be coming from the accusing parent, whose allegation will hold greater weight if it is not disputed.

It is always a good idea for the child to be seen for an independent forensic evaluation. This would be in addition to the child’s involvement with the court-appointed evaluator.

If this is the first allegation of abuse, and it occurs during a child custody case, its validity must be questioned. In fact, there is a significant probability that the allegation is false, as it is unlikely that a parent’s first abuse of the child occurs after the child custody case has been initiated. Thus, if a parent does not have a history of abusing the child, it is not likely that the first abuse is occurring during the legal proceeding.

A series of allegations against a parent during a child custody proceeding is also a major red flag. An accusing parent often believes that multiple allegations against the other parent are more convincing to a judge than a single allegation. However, repeated abuse of a child during a circumscribed time period during a child custody case, for example—is quite improbable.

Detecting a false allegation is easier with the use of a timeline. Marking the major occurrences in a child custody case can show the specific sequence of events. A false allegation of abuse may occur during the custody case, and not before. It may also occur in response to legal action taken by the other parent. For example, if a mother files for full custody of her child, this sets the stage for the father to report a false allegation of abuse against the mother with the hopes that the allegation will derail the mother’s quest. The motive of the false allegation can be detected by examining its place on the timeline of events.

False allegations of abuse often include unwitting help from the children. Children aged between 3 and 7 years can be easily coached by a parent to testify against the other. Because most children want to please their primary parent, they are easily swayed, cajoled, convinced, and brainwashed. It is difficult for children to know the truth once a parent has coached them extensively. False allegations can involve older children and teenagers as well, but their coaching is more easily transparent and adolescents may even admit to it.

There are 5 common beliefs that motivate a parent to lodge a false allegation of abuse against the other parent (Table). If any of these beliefs are discovered, the allegation of abuse is likely false. Detecting these beliefs in a parent requires careful interviews over several sessions. A parent will never admit to fabricating a false allegation. The clinician must be skilled to see through the defensiveness, deceitfulness, and/or distractions of an offending parent.

Harmful and false beliefs by the accusing parent can also be detected through interviews with the child and the accused parent. Usually, the child or the accused parent will provide critical clues as to the accusing parent’s belief system. Bits and pieces of information will fit together into a detailed narrative that exposes the falseness of the allegation at hand. Remember, the accusing parent generally does not recant nor apologize for their attempts at relationship interference.

Understanding the Process

Once an allegation of abuse has been declared by a parent, there is a process that should ensue.

First, the judge should appoint a psychiatrist or clinical psychologist to evaluate the child and both parents. This evaluation must include interviews, psychological testing, and a review of collateral data (eg, emails, texts, recordings, pictures, etc).

Table. Five Beliefs That Motivate False Accusations of Child Abuse

<table>
<thead>
<tr>
<th>Belief</th>
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<tbody>
<tr>
<td>1. “If you don’t want me, you don’t get your child either.”</td>
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<tr>
<td>2. “I’m scared our child will love you more than me and will want to live with you.”</td>
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<tr>
<td>3. “I hate you and I want to exact revenge on you.”</td>
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<tr>
<td>4. “I need my child too much to tolerate you having an ongoing relationship.”</td>
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<tr>
<td>5. “Our child has a stepparent now and you are not needed.”</td>
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The evaluator should have access to other independent assessments of the allegation, such as Department of Human Resources investigations or a forensic evaluation of the child.

The psychiatrist or clinical psychologist must be experienced in child custody evaluations. Similarly, there should be a wait-and-see attitude about the allegation until the evaluation process has been fully completed. In other words, no assumptions or decisions should be considered until all the facts and information have been collected and assessed. The evaluation by the mental health professional should be aimed at determining the validity of the stated allegation of abuse.

During this time, attorneys should not respond to an allegation of abuse by filing motions for dramatic or extreme action, such as obtaining full custody of the child. However, granting a parent temporary custody until the matter is settled may make sense, especially if the child’s physical safety is of acute concern. Similarly, the attorneys must not try to sabotage the evaluator in order to win their case. The evaluator’s conclusions and recommendations should be given strong weight in the judge’s final decision.

Implications of the Evaluation
A false allegation of abuse by a parent should be met with firm consequences, such as a fine, supervised parenting time, court-ordered counseling, and/or loss of primary custody. Swift and decisive consequences will dissuade future false allegations of abuse.

The accusing parent may not be appropriate for primary custody. Even shared custody may not be appropriate. A parent’s willingness to fabricate an allegation of abuse against the other parent is a poor prognostic indicator. It is not simply an accident or a mistake. A false allegation is an intentional and purposeful attempt to undermine the child custody proceeding.

Similarly, the false allegation has implications for the future well-being of the child, and a false allegation should be considered a form of parental alienation. This experience, especially if they are asked to take an active role in the allegation, teaches the child to be dishonest, deceitful, manipulative, conflictual, and blaming. Furthermore, the love the child should have for both parents is compromised and potentially destroyed.

A false allegation of abuse is serious, and it must be tolerated in the court system. Based on the consequences, a false allegation represents a psychiatric emergency. As such, it can be handled and dealt with in a direct and timely manner. A child’s mental health and well-being depend upon it.

Dr. Blotcky is a licensed clinical psychologist in private practice in Birmingham, Alabama. His forensic practice focuses on child custody and alienation cases. He is also a clinical associate professor in the Department of Psychology at the University of Alabama at Birmingham.

Strategies for Successful Medical Practices

Todd Shryock

Only 11% of medical practice owners said they did better in 2020 than in 2019, whereas 46% said they were doing worse, according to the Medical Economics® 2021 Physician Report. The top reason listed was lost revenue and increased expenses because of COVID-19. Here are some strategies to boost your practice’s bottom line.

Look at Performance Indicators
Successful practices track performance indicators to identify opportunities for improvement, said Andrew Hajde, assistant director of association content for the Medical Group Management Association. These indicators include accounts receivable, insurance claims, reimbursement, denials, and patient satisfaction.

With those data, practices can not only track their own performance over time, Hajde explained, but also benchmark themselves against data from similar providers. He added, “It gives them [practices] a bar to see if they’re doing well or if they have some opportunities for improvement in any of those areas."

Similarly, it is also important to find out what other practices are doing to get positive patient engagement and quality ratings, Hajde told Medical Economics. “That’s where it is critical to work with your peers across the country that are achieving those best practices via conferences [and] member communities with associations and [by] researching, reading articles, [listening to] podcasts, or any way you can get in front of how people are achieving those things to bring to your practice.”

Denials and Accounts Receivable
Additionally, thriving practices analyze their claims denials and take action to reduce them. It’s crucial to track which payers are denying claims and why they are doing so, Hajde said.

Likewise, Hajde suggested checking accounts receivable for possible causes. “Is it because you are not getting paid in a timely manner or that a lot of claims are being denied?” Hajde asked. To reduce denials, ensure information is entered correctly by office employees.

Claims should also be filed in a timely manner, and all denials that are deemed inappropriate should be appealed within the payers’ established deadlines. “Sometimes you only have 30 or 60 days, so make sure you are on top of that,” Hajde explained.

Regularly Review Payer Contracts
Every contract has unique details such as requirements for prior authorizations, medical necessity, and timely filing, in addition to the reimbursement agreement. Hajde recommended regularly reviewing contracts and payment rates. “I’ve talked to some practices that haven’t renegotiated with an insurance payer for 5 or 10 years,” he said, “and they are underperforming in terms of their payment rates.”

Also, verify payment compliance and do not assume the payer is always accurate. “Confirm the payment is actually for what your contracted rate is, because sometimes you are inadvertently underpaid,” he added.

Communicate Patient Expectations
Patients should be aware of which part of the payment is their responsibility and, if they cannot pay, how that will be handled, Hajde said. All payment policies and procedures also need to be clearly communicated to staff.

Rick Gundling, senior vice president of health care financial practices at Healthcare Financial Management Association, recommended surveying patients on how they wish to be contacted: text, phone, portal, or app. Different patient populations have different expectations, but knowing their preferred communication type can help with billing- and care-related messages. An online payment portal is vital because patients expect the convenience, and it can speed up payment, Gundling added.

Nurture a Positive Office Culture
“You really need to commit to customer service training to really create a high morale and great patient experience,” Hajde noted. “Patients really pick up on it, and anyone who’s been in a medical practice or other health care facility can tell when employees are dissatisfied. It doesn’t lead to a great experience. It won’t make patients want to tell their friends and family to go to this practice or organization.”

Read More
https://bit.ly/2TIWJk8
Important Safety Information

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

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

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

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

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

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

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

- **Leukopenia, Neutropenia, and Agranulocytosis** (including fatal cases). Perform complete blood counts in patients with pre-existing low white blood cell count (WBC) or history of leukopenia or neutropenia. Discontinue CAPLYTA if clinically significant decline in WBC occurs in absence of other causative factors.
Choose CAPLYTA to help control your patients’ symptoms—with a metabolic, weight, and EPS profile similar to placebo in 4- to 6-week trials¹

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

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

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

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

Please see the accompanying Brief Summary of Prescribing Information on the following page. Reference: 1. CAPLYTA prescribing information, 2019.

SEE ITS EFFICACY AT CAPLYTAHCP.COM
INDICATIONS AND USAGE
CAPLYTA is indicated for the treatment of schizophrenia in adults.

CONTRAINDICATIONS
CAPLYTA is contraindicated in patients with history of hypersensitivity reaction to lumateperone, other antipsychotics, add-on treatment with other antipsychotics, or lumateperone itself.

WARNINGS AND PRECAUTIONS
Increased Mortality in Elderly Patients with Dementia-Related Psychosis
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (mean duration of 6-10 weeks) of antipsychotic drugs in elderly patients with dementia showed a presenile dementia-related psychosis. CAPLYTA is not approved for the treatment of patients with dementia-related psychosis.

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COMMENTARY

A Clinician and a Poet:
Reimagining the 15-Minute Med Check

Ronald W. Pies, MD

Seventeen years ago, I published a piece in *Psychiatric Times* titled “The Poet and the Psychiatrist.” In the article, I alluded to “an unusual therapy group” I co-led as a resident nearly 40 years ago, in which psychiatric inpatients “… were encouraged to bring in poetry—whether their own or that of others—and read it to the group. A psychiatric nurse and I encouraged a discussion of the feelings, images, and memories the poems would almost invariably evoke.”

Poetry readings were often a space where patients who rarely expressed their feelings in the course of a formal therapy session felt they could speak freely. Sadly, the very idea of conducting such a group in today’s climate of truncated psychiatric care can seem quaint or naïve, at best. This point was brought home to me while reading February’s “Letter From the Editor,” in which *Psychiatric Times* Editor-in-Chief, John J. Miller, MD, detailed the economic pressures on psychiatrists over the past 30 years that have led to the now-infamous “15-minute medication check.”

Miller pushed back on this pro-crustean limit by suggesting—or, at least, imagining—that psychiatrists extend the session to 16 minutes. The extra minute, he suggested, could be used to gain some important personal information about the patient. Questions might include, for example, “Who do you feel had the greatest influence on you growing up?” or “When do you feel most at peace with yourself?” or “What do you do for relaxation?”

Riffing off his suggestion, I would like to propose another question we might put to certain suitable patients—a question I raise as both a clinician and a poet. But first, I would like to examine the whole notion of the medication check, with the aim of reimagining it as something more than a superficial exercise in refilling a script.

More Than 15 Minutes

For starters, I urge psychiatrists to resist the 15-minute med check model, wherever and whenever possible. I realize that will not be greeted with enthusiasm in most managed care settings, but I think there are good reasons—and compelling ethical imperatives—why we should push back hard. As child psychiatrist David Rettew, MD, succinctly put it:

> In 15 minutes…there is barely enough time to go over side effects, dose and medication changes, and informed consent, let alone engage in discussions about what may really be going on in a patient’s life and how a multitude of other possible interventions (improving sleep, exercise, nutrition, relationships) might be useful.

There is good reason to believe that resistance is not always futile. For example, Lorraine Roth, MD, commented in 2011:

> I retired from the VA last year and have worked a number of Locum Tenens positions since then. One was at a mental health clinic that needed a psychiatrist to cover for a few months. They stated that evaluations were 1 hour, med checks 15 minutes. I said I need 30 minutes. I explained that 15-minute checks are adequate for those patients who are “doing well, just need a refill,” but 30 minutes allows for the adequate evaluation and decision-making necessary for patients who are not doing well. In addition, it is essential to write a good progress note, and trying to include that in a 15-minute slot is not workable. They granted my request for 30-minute med checks.

The situation has probably worsened since Roth posted her comments a decade ago, and not all psychiatrists will have the leverage she apparently had. Still, I believe that serious pushback is worth a try.

Utilizing Every Second

If you must see each patient for only 15 minutes, try to find a way to humanize what might otherwise be a perfunctory, robotic encounter. For example, H. Steven Moffic, MD, explored the usefulness of asking med check patients, “What gives you meaning in your life?” Or, more colloquially, “What keeps you going?” Moffic asked patients to write out their answers prior to the 15-minute med check and found that this single question often elicited important information. He shared an encounter in which he posed that query to a patient with posttraumatic stress disorder (PTSD). The patient’s response was “nothing.” Moffic explained, “After I felt a chill, I asked if she felt suicidal, and she did. We changed her medication and increased the frequency of appointments.”

It is also important not to underestimate the need for psychodynamic understanding of the patient, even—or perhaps especially—in the brief space of a med check. Glen Gabbard, MD, has observed:

> Psychiatry has probably made far too much of a distinction between psychotherapy and pharmacotherapy in training and in practice. Psychotherapeutic skills are needed in every context in psychiatry because the same phenomena that emerge in psychotherapy—transference, resistance, countertransference, schema, automatic thoughts—appear in other contexts. All clinical work in psychotherapy depends on attending to the therapeutic relationship.

Miller made essentially the same point in his video “Making Psychotherapy Part of Every Psychiatric Visit,” noting that from the time you greet your patient in the waiting room to the time you escort them to the door as they leave, “everything you do is psychotherapy,” and “every microsecond is a personal interaction.” Indeed, sometimes a med check cannot move to completion until the patient’s hopes, fears, fantasies, and resistances are understood and explored.

Listen With the Third Ear

Please join me now in a brief thought experiment. Imagine you are able to negotiate with the powers that be, such that you can extend that nefarious 15-minute med check to 25 or even 30 minutes. Let us further imagine your patient: “Mr. Arnold,” a divorced, retired teacher, aged 70 years, with major depressive disorder, now in remission, whom you see twice a month for med checks. He has clearly benefited from his antidepressant (bupropion 250 mg qd), but he finds it very difficult to share any deep feelings during your meetings with him.

When you ask him, “How are you feeling?” he shrugs and says, “Not depressed like before, Doc. Just kind of blah.” He sees a psychiatric social...
worker twice monthly for supportive therapy and she reports a similar experience with Mr Arnold. “He’s not clinically depressed anymore,” she reports, “but he just seems very closed off and shut down, emotionally flat.”

You consider the possibility that his antidepressant may be causing this feeling, but—unlike the selective serotonin reuptake inhibitors—buproprion almost never causes this kind of emotional flattening. In your current session, you tell Mr Arnold that you have often found it helpful to use poetry in your work with patients. You then ask him one simple question: “Mr Arnold, would you be interested in using poetry to help change that blah feeling?” He seems dubious at first but says he will give it a try.

Playing out this thought experiment: Might you be able to use your expanded 25-minute med check appointment to bring poetry into the clinical context? For example, could you ask Mr Arnold to select a poem that is meaningful to him and then allow for 5 to 10 minutes to read and discuss the poem? This might be an occasion, as Theodor Reik, PhD, would have put it, to “listen with the third ear...attending to vague impressions, intuitions, images, associations, and even memories.”

Indeed, in my experience, the patient’s very selection of the poem can be central to the treatment. As Berlin has written, “Doctors need poetry to bring them closer to their patients...Poetry can help doctors become better healers because poems teach us to see the world from the emotional viewpoint of another person.”

I believe that psychiatrists who engage with poetry in their clinical work will come to understand what William Carlos Williams, MD, meant when he wrote:

“It is difficult to get the news from poems / yet men die miserably every day / for lack of what is found there.”

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REFERENCES
The Snake Pit: What One Film Did for Psychiatry

Greg Eghigian, PhD

Hollywood has taken great interest in psychiatry, psychoanalysis, and psychotherapy over the decades. As a result, the general public has come to view the work of clinicians by way of films, including one of the most influential films of the mid-20th century: 1948’s The Snake Pit.

The film has been the subject of a great deal of scholarly debate, criticized for its portrayal of its female protagonist, her fellow patients, and hospital staff. Recently, Ben Harris, PhD, emeritus professor of psychology at the University of New Hampshire, published “The Snake Pit: Mixing Marx With Freud in Hollywood” in the journal History of Psychology, using archival sources to revisit the film’s making and reception. Harris, who has also held postdoctoral fellowships in the history of science and medicine at the University of Pennsylvania and the University of Wisconsin, sat down with Psychiatric Times to discuss his findings.

**Psychiatric Times**: For those who may be unfamiliar with it, will you recap The Snake Pit?

**Ben Harris, PhD**: The award-winning film showed the hospitalization and recovery of Virginia Cunningham at an upscale New York psychiatric hospital. A confused but resilient young woman, Virginia progresses through various overcrowded, understaffed wards to Ward 1—the best. She then relapses and ends up in Ward 33—overflowing with the most disturbed patients. This seems to her like a medieval snake pit, into which the mad were tossed to shock them into health.

Realizing that she is healthier than the worst-off patients, Virginia gradually regains her sanity. She is aided by the saintly Dr Mark Kik, who uses electroconvulsive therapy to connect with Virginia, followed by “narcosynthesis” and then psychotherapy informed by Freud. As her childhood fixations are unearthed and her transference to Kik is resolved, Virginia comes to love her husband again, whereas before she had denied his existence.

Throughout her hospitalization, Virginia connects with fellow patients who struggle with their illness and the uncertainties of the post-WWII era. Olivia de Havilland’s portrayal of Virginia earned her an Academy Award nomination and landed her on the cover of Time magazine.

**Eghigian**: Over the years, the film has received backlash. What have been the main critiques?

**Harris**: Critics in women’s studies saw the female staff in the psychiatric hospital as single and, thus, emotionally incomplete—propaganda that women would only find happiness and their true nature in marriage and home life. There were also complaints that the film gave Virginia a Freudian complex, the resolution of which required the help of a male therapist.

**Eghigian**: Meanwhile, both viewers and reviewers of the film saw it quite differently.

**Harris**: Mainstream critics saw it as emotionally gripping and recognized it as the first film to portray mental illness in a nonsensationalized form. Its overall impact was reflected by Time putting Olivia de Haviland on its cover.

Despite the Freudian subplot, political progressives saw it as positive propaganda for bettering the conditions of a neglected group: the mentally ill. Thus, the Communist Party’s West Coast daily said it was “a film achievement” that called for hospital reform rather than “new regiments of psychoanalysts.”

**Eghigian**: Many people who have seen The Snake Pit are unaware that it was a novel before it was a film. You have delved into the life of its author, Mary Jane Ward. What can you tell us about her?

**Harris**: In both the film and Ward’s novel, Virginia rebelled against the bureaucratic rules and antitherapeutic attitudes of many of the staff. She had a wicked sense of humor and, in the book, she was antiracist and a socialist—as Ward was in real life. In the book, she came to dislike the Freudian views of her therapist, while in the film she came to resolve her emotional problems through talk therapy.

In real life, conflict over giving a pacifist speech precipitated Ward’s first breakdown. Also, her relationship with her therapist reawakened unconscious conflicts over a boyfriend who had died. However, her therapist (who trained with Dr Frieda Fromm-Reichmann) judged that she was psychologically too fragile to undergo talk therapy that would uncover repressed material.

**Eghigian**: One of the more intriguing things you did was to look at unpublished correspondence and drafts of the film’s screenplay to get a fuller view of those involved in the production of the film. What did you learn by looking at these materials?

**Harris**: The correspondence shows how closely the screenwriters worked with prominent psychiatrists on the plot and its details. One can also see the political consciousness and solidarity that existed among Hollywood screenwriters, some of whom would soon be blacklisted.

My most stunning discovery was the last scene in the film, which was originally created by the screenwriters but replaced secretly by the producers. It showed Virginia to be socially conscious, pledging to continue the struggle for reform from the outside. This was replaced by a saccharine, antifeminist scene in which Virginia asks her husband to restore her wedding ring to her finger as they leave the hospital.

**Eghigian**: You note that 2 of the film’s screenwriters visited a state hospital and talked to staff and patients. Do you have a sense of how this affected their approach to the project?

**Harris**: Building on the novel’s details, I think it helped them convey the sights and sounds of a huge, custodial institution in which keeping order was conformity, but just the opposite. How so?

**Harris**: Consistent with the antifascist spirit of World War II, we see patients rebelling against authority that is arbitrary, such as the rule that no one in the back ward can step on “the rug.” Rather than accept the socioeconomic status quo, patients used humor to express their fears about the postwar economy and their posthospital lives. Finally, in preparation for her discharge, Virginia hands off the care of a disturbed young woman that she has been looking out for to another fellow patient. This provided a collectivist touch that was the opposite of deferring to male physicians.

**Eghigian**: What do you believe is the legacy of the film?

**Harris**: I began my research believing that the film raised the consciousness of the public about mental illness. It took a New York Times obituary for Charles Schlaifer to make concrete the film’s direct impact on mental health policy and care. Schlaifer, who appears nowhere in the history of psychiatry, was a publicist at 20th Century Fox. He did the publicity for The Snake Pit and learned in detail the problems facing the mentally ill.

He became an advocate for mental health reform in the 1950s, including greater funding for research. He used his publicist skills to become a highly effective Washington lobbyist and advocate, welcomed to Congressional hearings based on his work on The Snake Pit.

**Dr Eghigian is professor of history at Penn State University. He specializes in the history of psychiatry and mental health and is member of the Psychiatric Times Editorial Board.**

**REFERENCES**


Medication Decisions for Women of Childbearing Potential

David N. Osser, MD

Medication decisions during pregnancy are always a challenge, and, since many pregnancies are unplanned, considerations should start well before pregnancy occurs and should be addressed again if the patient becomes pregnant. Patients with bipolar disorder who stop medication during pregnancy can have a relapse rate of 80% for depression, 16% for mania, and 4% for mixed episodes during the postpartum period (Figure). However, many bipolar medications can have harmful effects during pregnancy.

Ranking Treatment Options
Valproate is the most teratogenic bipolar medication and should be avoided in women of childbearing potential until all other options have been exhausted. Use of valproate in pregnancy has been a source of concern internationally. Valproate (but not lamotrigine) also is associated with lower intelligence scores in young children who were exposed to it in utero and is associated with an elevated risk of autism spectrum disorder and attention-deficit/hyperactivity disorder.

Carbamazepine is almost as teratogenic as valproate and is associated with increased spina bifida and vitamin K deficiencies late in pregnancy. The data on lamotrigine suggest low risk of fetal harm as monotherapy, but cleft palate is a concern.

Lithium has fewer malformation risks than valproate and carbamazepine. In a large study, the adjusted risk ratio for any cardiac abnormality was 1.65 compared with unexposed babies. The risk rises with higher doses, but it still has been shown to be lower than previously thought. For Ebstein’s anomaly, the risk ratio was 2.66. In absolute numbers, the risk was 0.6% for lithium-exposed infants vs 0.18% for those not exposed. In the most recent meta-analysis, the absolute risk of any cardiac abnormality was 1.2%. The increased risk was limited to lithium exposure in the first trimester.

Note that these observational studies involved comparisons of women with bipolar disorder taking lithium vs those not taking lithium. Rates of cardiac abnormalities are lower in women without bipolar disorder. The study results were often unclear if they excluded women who were on other teratogenic medications or were misusing any substances like alcohol. The authors concluded that the risks of lithium exposure during pregnancy are low. The risks associated with mood episode relapse following lithium cessation or lowering the level below the therapeutic range appear, for most women, to exceed the harms of fetal abnormalities or other pregnancy complications associated with continuing lithium.

Thus, lithium is preferred over valproate and carbamazepine. For some patients, lithium should be the first choice. For bipolar depression, the second-generation antipsychotics (eg, lurasidone, quetiapine, cariprazine) are reasonable choices, although the data on safety in pregnancy for the newer drugs are limited. Depot antipsychotics should not be routinely used in pregnancy; infants may show extrapyramidal symptoms for months. Anticholinergic drugs should not be prescribed to pregnant women except for acute, short-term need. Antipsychotics in pregnancy seem relatively safe with respect to congenital malformations.

There is a high risk, however, of gestational diabetes with olanzapine (the second worst option is quetiapine).

Electroconvulsive therapy (ECT) during pregnancy warrants more caution than previously thought. It causes fetal heart rate reduction, uterine contraction, and premature labor in up to one-third of cases. In a large survey of case reports, ECT was found to have a child mortality rate of 7%. ECT can be used for severe depression, catatonia, medication-resistant illness, extremely high risk for suicide, psychotic agitation, and severe physical decline due to malnutrition, dehydration, or other life-threatening conditions.

Recommendations
Avoid valproate in any woman with the potential to become pregnant. Should the patient become pregnant, it may be too late to discontinue it before harm is done. High-dose folate (4-5 mg daily) has been recommended if valproate or carbamazepine are essential, but the protective effect occurs only if used prior to conception.

Lamotrigine may be considered for bipolar depression. Prescribe as few drugs as possible—ideally only 1 medication. When pregnancy unexpectedly occurs during treatment, it is usually best to continue the regimen to avoid exposure to additional agents—except if the patient is on valproate or carbamazepine. In such cases, switching to something safer should be considered. Adjust doses as pregnancy progresses. Blood volume expands 30% in the third trimester. Plasma level monitoring is helpful.
Although psychosis often emerges relatively early in life, it can also appear for the first time in older patients. These cases raise special challenges. The morbidity and mortality rates for psychosis in late life are significantly greater when compared with those for psychosis among younger individuals. Furthermore, greater incidence of adverse effects is noted when antipsychotic medications are prescribed to older adults. But once clinicians determine the root of the problem, they have an array of potentially effective treatment options.

Primary and Secondary Disorders
In identifying psychotic disorders in late life, a distinction must be made between primary psychotic disorders and secondary psychotic disorders. The term primary psychotic disorders describes conditions in which the psychotic symptoms are the main clinical presentation of the illness. Primary psychotic disorders include illnesses along the schizophrenia spectrum, major depressive disorder (MDD), and bipolar disorder with psychotic features.

The term secondary psychotic disorders refers to illnesses in which psychosis is the secondary or associated symptom, not the core clinical feature of the disorder. Examples of secondary psychotic disorders including delirium, neurocognitive disorders, psychosis due to drugs of abuse or prescribed medications, or psychosis due to medical or neurological disorders. Available evidence indicates that among older adults, approximately 60% of the cases are secondary disorders.

Diagnosis
A thorough history, including information from collateral sources, can help differentiate between primary and secondary causes. Acute or subacute onset of symptoms might suggest the occurrence of delirium or of substance- or medication-induced psychosis. Insidious onset of symptoms may suggest a primary psychotic disorder, such as a schizophrenia spectrum disorder.

Features suggestive of a secondary psychotic disorder include an atypical age of onset of symptoms, visual hallucinations presenting independently of auditory hallucinations, the occurrence of psychotic symptoms in an individual with no previous psychiatric history or no family history, the presence of abnormal findings on physical examinations, or evidence of the use of prescribed medications or abuse of illicit substances. The Figure describes a workup for psychotic disorders in late life.

Exploring Treatment Strategies
For secondary psychotic disorders, the initial treatment involves addressing possible causes, including the discontinuation of offending medications or drugs of abuse or the treatment of underlying medical or neurological causes. For psychotic symptoms that are unresponsive to these strategies, pharmacological treatment becomes essential. Antipsychotic medications should be prescribed to older adults cautiously, as their long-term use may cause significant adverse effects. Available guidelines recommend the short-term use of antipsychotics to treat the psychotic symptoms. Before initiating treatment with antipsychotic medications, clinicians should always perform a risk-benefit analysis, keeping in mind the individual’s physical condition and comorbid medical disorders. Starting medication at a lower dose (one-fourth to half the starting dose for adults) and gradually titrating to the optimal dose may reduce the incidence of adverse effects.

Available evidence indicates that risperidone and olanzapine may be useful in the treatment of older adults with schizophrenia. One randomized controlled trial study that evaluated the use of amisulpride (not available in the United States) at 100 mg daily in patients who were diagnosed with late-onset schizophrenia found a significant improvement in the Brief Psychiatric Rating Scale compared with placebo. There is also some evidence for using paliperidone among older adults with schizophrenia. Expert consensus guidelines recommend using risperidone at 1.25 mg to 3.5 mg a day as the first-line agent for older adults with schizophrenia, followed by quetiapine at 100 mg to 300 mg a day, olanzapine at 7.5 mg to 15 mg a day, or aripiprazole at 15 mg to 30 mg a day. There is little support for using clozapine among older individuals with psychotic disorders, possibly due to its significant adverse effect profile.

Among older adults who have MDD with psychotic features, the combination of olanzapine and sertraline was associated with higher remission rates during the treatment period when compared with treatment with olanzapine or placebo, with good tolerability noted for the medication combination. In a systematic review of meta-analyses that evaluated the use of antipsychotics among individuals with dementia, the investigators found that antipsychotics had modest efficacy in treating psychosis, aggression, and agitation. The use of these medications was often limited by their AE profile. The investigators noted that the use of antipsychotics should be reserved for severe symptoms that have failed to adequately respond to nonpharmacological management strategies.

A meta-analysis that evaluated the prevention and treatment of delirium among surgical and medical patients found that antipsychotics had limited efficacy in treating delirium. There is also significant controversy regarding the use of antipsychotics among older adults who present with severe psychosis due to dementia. The FDA has a boxed warning indicating an association between the use of antipsychotics among older adults with dementia and increased risk for mortality. Additionally, the use of antipsychotics in this patient population increases the risk for cerebrovascular adverse events, metabolic side effects, and pneumonia, when compared with age-matched controls who were not prescribed these drugs.

Antipsychotic medications should be gradually titrated to the optimal dose.
Bilateral electroconvulsive therapy has been found to be a safe and effective treatment for older patients with schizophrenia, in conjunction with antipsychotic medications, especially among those individuals who present with catatonia, agresssion, or acute suicidal states, when there is an acute onset of symptoms.

Available data indicate efficacy for cognitive behavioral social skills training(CBST), functional adaptation skills training (FAST), supported employment, social skills training, and preventative health care programs among older individuals with psychotic symptoms. 

Additionally, better work outcomes and superior quality of life were noted for older individuals with schizophrenia who received supported employment when compared with conventional vocational rehabilitation programs. The Table describes further treatments for psychotic disorders arising in late life.

Concluding Thoughts
Most cases of psychotic disorders in late life likely occur due to underlying medical or neurological illnesses and/or due to the effects of medications or illicit drugs. The differentiation of primary and secondary causes can be accomplished via a thorough history, a comprehensive mental status examination, appropriate laboratory data or imaging studies, and a formal neuropsychological assessment for difficult-to-diagnose cases.

The use of antipsychotic medications among older adults is fraught with risks given these drugs’ significant adverse effect profile, including the increased risk of death among individuals with dementia. It is recommended that antipsychotic medications be used among older adults in the lowest effective doses for and the shortest time period.

The early identification and prompt removal or treatment of secondary causes of psychosis will reduce undue suffering among vulnerable older adults. Psychosocial treatments have been found to be effective in the treatment of primary psychotic disorders among older individuals. Future studies should focus on the risk factors, neurobiology, and treatment of psychotic disorders in late life, so that we better understand and treat these varied group of disorders.

Dr Tampi is professor and chairman, Department of Psychiatry & Behavioral Sciences, Cleveland Clinic Akron General, and Chief, Section for Geriatric Psychiatry, Department of Psychiatry and Psychology, Cleveland Clinic.

References

Do you have an interesting hobby or travel experiences you’d like to share with your colleagues? Do you find volunteer work fulfilling and want to share what you’ve learned and what you do? Psychiatric Times® is proud to present the new video series “More Than Medicine” to share the activities you and your colleagues enjoy when the clinical work is done—riding horses to painting to building homes for the homeless.

If you are interested in sharing your story, write to us at PTEditor@mmhgroup.com.
Expert Perspectives on Recognition and Management of Tardive Dyskinesia

Xavier highlighted that antipsychotic medications are used for both primary psychiatric disorders and mood disorders, including bipolar disorder, and as adjunctive treatment for major depressive disorder. Though the atypical antipsychotics commonly used today carry less risk for tardive dyskinesia (TD) than earlier agents, faculty agreed that the risk of TD remains significant with atypical agents. Citrome said that atypical antipsychotics block postsynaptic dopamine-2 receptors, the putative mechanism underlying the development of TD.

Treating TD is not as simple as stopping the antipsychotic agent, particularly if it is keeping a patient stable. “We need to look at interventions that allow us to continue ongoing treatment for the underlying psychiatric disorder. The option in my mind would be a VMAT2 inhibitor (vesicular monoamine transporter type-2 inhibitor), of which 2 are approved by the FDA for the treatment of tardive dyskinesia, which is added to the patient’s ongoing regimen,” said Citrome.

Symptom Recognition and Impact on Patients

Faculty cited some of the movements that are characteristic of classic TD: fingers moving as if playing the piano, shoulder shrugging, facial grimacing, tongue protrusion at random times, chewing, and blepharospasm. Oftentimes, symptoms of TD are reported by family members or case managers.

According to Citrome, though patients with mood disorders are often more insightful about abnormal movements, those with schizophrenia can also become aware of these movements. This can lead to heightened anxiety, paranoia, and social isolation. “When we’re trying to transition someone back into the community, it’s really very stigmatizing to have these abnormal movements that set you apart from other people,” he noted. Xavier emphasized the importance of considering the level of distress that patients experience from TD. Citrome agreed, acknowledging that what providers consider to be mild TD can be viewed as severe by the patient and significantly disrupt their ability to function and interact with others.

Diagnosis of Tardive Dyskinesia

Before starting any antipsychotic (dopamine-2 receptor blocking agent), and every 6 to 12 months while taking an antipsychotic, the patient should be screened for abnormal movements. “The Abnormal Involuntary Movement Scale [AIMS]…is the gold standard,” said Citrome. He briefly described the AIMS, emphasizing that the tool is very helpful for distinguishing TD symptoms from drug-induced parkinsonism as well as a range of other movement disorders.

Citrome and Xavier agreed that if necessary, the AIMS can reliably be performed via telepsychiatry visits. Citrome noted that recording the video and zooming in can be helpful for confirming abnormal movement. He further added that “it’s helpful to have someone there with the patient, holding the camera, holding the phone from a distance.”

Aside from the AIMS, other clues can help inform the diagnosis of TD. “If [the abnormal movement] emerges a year or 2 [after initiating treatment with a dopamine-2 blocking agent], and they didn’t have any problems before then, we’re going to be very suspicious of tardive dyskinesia,” according to Citrome. He also mentioned an additional clue to correct diagnosis, stating, “If we lower the dose of the antipsychotic, the drug-induced parkinsonism should get better, but the TD may look a little worse.”

Guideline-Directed Treatment of Tardive Dyskinesia

With their most recent guideline for the treatment of schizophrenia, the American Psychiatric Association recommends the use of VMAT2 inhibitors for treatment of moderate to severe TD. “The recommendation extends to patients with any degree of TD if the movements result in functional impairment that the patient or their care providers are aware of.2 “The level of evidence is pretty strong that VMAT2 inhibitors actually do work well for tardive dyskinesia symptoms,” noted Xavier. Citrome concurred, highlighting that VMAT2 inhibitors produced rapid (within 6 weeks) and durable reductions in TD symptoms in clinical trials.

Both FDA-approved agents, deutetrabenazine and valbenzamine, reversibly inhibit VMAT2, a transporter that regulates dopamine uptake from the cytoplasm to the presynaptic vesicle for storage and release into the synapse.3 When that neuron is activated, the vesicles migrate to the presynaptic membrane, where they fuse and deposit the dopamine into the synapse, allowing dopamine to diffuse across the synapse to activate the postsynaptic dopamine-2 receptors. If the VMAT2 transport pump is blocked by the VMAT2 inhibitor, dopamine is depleted from the vesicles, resulting in a decrease in dopamine released into the synapse. This ultimately results in a decrease of dopamine agonism of the postsynaptic dopamine-2 receptors, which has the ultimate effect of decreasing the TD movements. According to Xavier, structured and ongoing assessment is important for monitoring response to VMAT2 inhibitor therapy.

Conclusion

Diagnosis of TD should be based on a formal, structured assessment of abnormal movements, and guidance on whether to treat should stem from how symptoms are affecting the patient. With the advent of VMAT2 inhibitors, “the door is open to the treatment of tardive dyskinesia from mild on up for people who need it, and the treatment guidelines certainly encourage us to do so,” Citrome concluded.

REFERENCES

Expert Perspectives on Recognition & Management of Tardive Dyskinesia

In this custom video series, experts Leslie L. Citrome, MD, MPH; and Rose Mary Xavier, PhD, MS, RN, PMHNP-BC; discuss appropriate management of antipsychotic-induced tardive dyskinesia.

They present a detailed analysis of three case studies, share insights on diagnosis and severity assessment, consider alternatives to anticholinergic medications, and examine VMAT2 inhibitors available for use to treat patients.

Watch it now: psychiatrictimes.com/td-perspectives
Fibromyalgia: What It Is and How to Treat It
Steven A. King, MD, MS

Fibromyalgia (FM) is one of the most controversial diagnoses in the field of pain management. Some experts believe that it does not exist and actually represents an accidental or purposeful misdiagnosis of other conditions, while others believe that it is badly underdiagnosed.¹

The truth likely falls somewhere between these 2 extremes. FM is certainly a real syndrome, but it is also perhaps overdiagnosed, both because many physicians are unaware of the actual diagnostic criteria, and because there may be a desire to avoid diagnosing patients with other conditions that could explain the symptoms of FM—most notably mental disorders.

Fibromyalgia Diagnosis Through the Years
Over the years, the medical understanding of FM has evolved. It has gone from being viewed as a pain disorder to being considered a multisymptom syndrome that falls on a continuum, depending on the number and severity of the symptoms.²

There are no universally agreed-upon definition diagnostic criteria for FM. At minimum, it is generally agreed that there is chronic pain spread throughout the body. However, even here there is some ambiguity. For example, the current International Statistical Classification of Diseases and Related Health Problems (ICD-10) diagnosis for FM says it can be “an acute, subacute, or chronic” painful state, although it also describes FM as “a chronic disorder.”³

What appears to have been the first attempt to develop formal diagnostic criteria was presented by Smythe and Moldofsky in 1977.⁴ Because of the many competing definitions of FM that emerged over time, the American College of Rheumatology (ACR) sought to develop a clear set of diagnostic criteria, which it issued in 1990.⁵ The most significant criteria were that 1) generalized pain was present for at least 3 months; 2) the pain was present in at least 3 of 4 body quadrants; and 3) the patient had pain to pressure of up to 4 kg/cm² as measured by an algometer at more than 11 of 18 points throughout the body.

The establishment of formal criteria resulted in FM being included as a diagnosis in the ICD in 1992. However, over the years, concerns grew about using these criteria, especially the identification of tender points, because it appeared that many physicians did not know how to accurately determine their presence or how much pressure to apply to elicit pain.

To address these concerns, the ACR revised its criteria in 2010.⁶ The requirement for tender points was eliminated, and the ACR instead based the diagnosis primarily on 2 scales: The Widespread Pain Index (WPI) and the Symptom Severity scale (SS). The WPI asks whether pain has been present level for at least 3 months; and 2) asking about the presence of any of 41 potential symptoms, including depression, fatigue, constipation, diarrhea, rash, chest pain, and headaches during the previous week and adding the total number of symptoms to obtain a score.

A diagnosis of FM requires either a WPI score ≥ 7 and SS ≥ 5 or a WPI between 3 and 6 and SS scale score ≥ 9.

<table>
<thead>
<tr>
<th>Table 1. American College of Rheumatology 2010 Diagnostic Criteria for Fibromyalgia⁶</th>
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<tbody>
<tr>
<td><strong>Widespread Pain Index (WPI) ≥ 7</strong> or <strong>Symptom Severity (SS) scale score ≥ 5</strong> or <strong>WPI 3–6 and SS scale score ≥ 9</strong></td>
</tr>
<tr>
<td><strong>Symptoms have been present at a similar level for at least 3 months</strong></td>
</tr>
<tr>
<td><strong>The patient does not have a disorder that would otherwise explain the pain</strong></td>
</tr>
</tbody>
</table>

ACTIVITY GOAL
After reading this article, clinicians should be able to identify the symptoms of fibromyalgia and have several options for distinguishing fibromyalgia from conditions with similar symptoms.

LEARNING OBJECTIVES
1. Recognize the difficulties in diagnosing fibromyalgia in the presence of mental disorders
2. Learn about the current recommendations for treating fibromyalgia

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Since the development of the 2010 ACR criteria, the work group has published 2 revisions. The 2011 revision recommended modifying the SS scale so that it could be self-administered by patients and not require physicians to determine the presence or extent of the severity of the pain. The 41-item checklist was replaced with a score representing the sum of scores for 3 items: headaches; pain or cramps in the lower abdomen; and depression symptoms. The authors created a fibromyalgia symptom scale that combined elements of the WPI and SS. It inquired about the locations of pain, the presence and severity of fatigue, the presence of pain or cramps in the lower abdomen, and the presence of depression and headaches. The most recent suggested revisions were published in 2016. The major recommended changes were that although FM could still be diagnosed with a WPI less than 7 and SS greater than 5 (the 2010 criterion), it could also be diagnosed with a WPI between 4 and 6 and an SS greater than 9. It also recommended adding criteria of generalized pain in at least 4 of 5 regions (left upper, right upper, left lower, right lower, axial) with jaw, chest, and abdominal pain not included, and symptoms being present at a similar level for at least 3 months.

The greatest change in the 2016 revision was the recommendation that a diagnosis of FM should not require the exclusion of other illnesses that could present with similar symptoms. These recommendations have yet to be formally adopted, and I have great concerns about allowing FM to be diagnosed along with other disorders that can cause widespread pain and other similar symptoms—most notably mental health disorders. I believe that FM is already overdiagnosed, and if it is diagnosed despite the presence of other conditions, then it could become the focus of clinical attention while other conditions that need to be treated may be largely ignored.

A more recent proposal for diagnostic criteria was developed by ACTTION (an acronym for a public-private partnership of a study network for analgesic, anesthetic, and addiction and the US Food and Drug Administration [FDA]) and the American Pain Society (APS). It was published in 2019.

The ACTTION APS Pain Taxonomy criteria include (1) multisite pain defined as pain at 6 or more of a possible total 9 sites (head, left arm, right arm, chest, abdomen, upper back and spine, lower back and spine including buttocks, left leg, right leg); (2) moderate to severe sleep problems or fatigue; and (3) the pain and fatigue or sleep problems must have been present for at least 3 months. Although the criteria note that the presence of another pain disorder does not rule out the diagnosis of FM, it does recommend a clinical assessment to evaluate for any condition that could account for the symptoms or contribute to their severity.

The ICD-10 criteria for FM are largely descriptive, calling it “a chronic disorder of unknown etiology characterized by pain, stiffness and tenderness in the muscles of neck, shoulders, back, hips, arms, and legs. Other signs and symptoms include headaches, fatigue, sleep disturbances, and painful menstruation.” It also notes that it is characterized by “multiple points of focal muscle tenderness to palpation (trigger points)” and that “Fibromyalgia makes you feel tired and causes muscle pain and ‘tenderpoints.’”

Which set of criteria is the correct or best one remains an open question. When examining patients who I believe may suffer from FM, I have continued to examine for tender points in addition to using the WPI and SS scales. Mental disorders are possible etiologies for widespread pain but are commonly overlooked. With this in mind, I make sure to evaluate for their presence and do not, as is commonly done, simply write off depression and anxiety as only being due to the pain. Unfortunately, as most pain specialists in this country are rheumatologists and FM has, for the most part, been considered the province of rheumatologists, careful evaluation for mental health disorders is likely to be rare.

**Etiology**

The etiology of FM remains unclear. For decades, it was viewed as a musculoskeletal or rheumatologic disorder. More recently, it is being considered a neurologic disorder, in large part because the medications that were found to be most efficacious for treating FM were those that were also most effective for neuropathic pain syndromes. The present thinking is that FM is most due to some form of central nervous system dysfunction, resulting in increased sensitization to pain. However, why it develops in certain individuals but not others largely remains a mystery.

**Demographics**

Measurements of the prevalence of FM have varied because of the different diagnostic criteria used to diagnosis it. Estimates have varied from 1.2% to 5.4%. Another major problem is that only about 25% of patients who report having FM have actually been diagnosed by a physician, and many of those who are diagnosed do not actually meet any formal diagnostic criteria for it.

Although FM is considered to occur more frequently in women, there is debate about the degree to which this is true. There is some concern that because women appear to be more likely than men to complain of pain to their health care providers, they are therefore more likely to receive the diagnosis. There is also an ongoing debate about whether pain is taken less seriously in women than in men and whether women are more likely to be simply given the diagnosis of FM, rather than receiving a full work-up to determine the presence of any underlying conditions that might be causing the pain. Furthermore, the female-to-male ratio has varied widely depending upon which diagnostic classification has been employed.

Being middle-aged or older appears to increase risk. However, FM can occur at any age, and some reports suggest that a juvenile form of FM might exist.

The presence of musculoskeletal disorders has also been reported to be a risk factor. However, there is the question of whether in at least some cases the symptoms of musculoskeletal disorders might be confused with those of FM. Other possible risk factors include high body mass index (BMI), cigarette smoking, and performing heavy or repetitive work (Table 2).

What have been described as bidirectional relationships (ie, each appears to be a risk factor for the other) between FM and migraine headaches, irritable bowel syndrome, gastroesophageal reflux disorder, and diabetes have been reported.

**Disorders With Similar Symptoms**

There are no objective tests to make the diagnosis of FM, so it is essentially a diagnosis of elimination, where other possible explanations for widespread pain are considered and ruled out. Because pain is such a common symptom, disorders of virtually every organ system can result in the symptoms of FM (Table 3). Many of these other conditions include symptoms that are not a part of FM and there are usually abnormalities on diagnostic tests. Notably, these include systemic inflammatory rheumatic diseases that, in addition to widespread pain, can present with other physical symptoms including skin rashes, vasculitis, and adenopathy, as well as with abnormal erythrocyte sedimentation rate and C-reactive protein, and joint abnormalities on radiographic imaging. Endocrine and infectious disorders, including thyroid abnormalities and hepatitis C, also present with additional symptoms and can be diagnosed with laboratory tests. Many medications have widespread pain as an adverse event. These include statins, opioids, chemothapeutic agents, and bisphosphonates. If patients are taking any of these, the pain would be considered likely to be secondary and, depending on the severity of the pain, alternative medications would be considered if available for the primary condition.

The most difficult disorders to differentiate from FM are mental disorders that also cause widespread pain. Obviously, there are no objective tests to make these diagnoses, which means that clin-

**Table 2. Purported Risk Factors**

<table>
<thead>
<tr>
<th>Female</th>
<th>Middle aged and older</th>
<th>Presence of musculoskeletal disorders</th>
<th>Anxiety/depression</th>
<th>Sleep disorders</th>
<th>High body mass index</th>
<th>Cigarette smoking</th>
<th>Lower educational level and lower socioeconomic status</th>
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**Table 3. Conditions With Similar Presenting Symptoms**

| Systemic inflammatory rheumatic diseases | Nonrheumatic musculoskeletal conditions | Nonrheumatic medical conditions | Endocrine/metabolic | Gastrointestinal | Infectious diseases | Malignancy | Neurological diseases | Myopathy/myositis | Psychiatric disorders, including depressive and anxiety disorders and posttraumatic stress disorders |
convulsant pregabalin. It should be noted that other medications have been found to be beneficial.

Whether the FDA-approved medications are more efficacious than others with similar modes of action is an open question, as there is scarce research comparing the various medications to one another. Most of the studies demonstrating the efficacy of these other medications were performed after the drugs were no longer under patent, so there was minimal financial benefit for manufacturers to formally seek approval of these for treatment of FM.

Whether amitriptyline is more effective for FM than other TCAs is also unknown. The strong sedative effect of this medication, which may be beneficial for sleep problems experienced by many with FM, may provide some advantage over less-sedating TCAs.

Nonsteroidal anti-inflammatory drugs may provide some benefit for FM but appear to be less efficacious than the SNRIs and anticonvulsants. One class of medications that is frequently prescribed to patients with pain, opioids, appears to provide little benefit to FM patients. The risk for adverse events associated with the use of opioids, most notably opioid abuse, is considered to outweigh whatever benefit they might provide.

A limitation of virtually all the studies on medications is that most report short- or medium-term results, leaving open the question of long-term efficacy, which is an important issue, considering that FM is a chronic condition.

Nonpharmacologic Therapies. Of the nonpharmacologic therapies, 2 appear to be especially efficacious. The first is aerobic exercise, which can be beneficial for many chronic pain conditions. Unfortunately, because patients may experience increased pain as they begin to exercise, they may take this as a sign that the exercise is exacerbating the pain and thus an indication to do less exercise. It can be helpful for patients to work with physical and occupational therapists, as these professional can instruct patients in proper ways to exercise and encourage them to continue (even if they initially experience increased pain) and in methods to perform daily activities that are less likely to exacerbate the pain.

The second nonpharmacologic therapy is cognitive behavioral therapy (CBT). Patients with FM can often benefit from CBT by focusing on the ways pain and other symptoms interfere with their lives and addressing these.

Patients may resist referral for CBT out of fear that benefiting from any form of psychotherapy indicates their health care providers believe they are suffering from a mental disorder and therefore their pain is not real. Providers need to explain that undergoing CBT is no way discounts the presence of the pain and other symptoms.

A major benefit of both exercise and CBT is that they are essentially free from adverse events and therefore unlikely to exacerbate FM and symptoms, something that can occur with medications.

Concluding Thoughts

Fibromyalgia has gone from being viewed simply as a pain disorder to being considered a complex, multisystem disorder, with widespread pain being only one of its symptoms. It is important to be aware of the diagnostic criteria for FM because other disorders, especially mental disorders, are not uncommonly misdiagnosed as FM. Finally, despite the variety of therapeutic options available, FM remains very difficult to treat.

Dr King is in private practice in Philadelphia, Pennsylvania.

REFERENCES


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Evan Feldman, M.D. | Medical Director, DMH
Evan.Feldman@dhhs.nj.gov  |  609.913.5516
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 Solhkhah, M.D., program director for psychiatry as well as founding Chair of Psychiatry & Behavioral Health at the Hackensack Meridian School of Medicine at Seton Hall University. “Our new psychiatry residency program will improve clinical care and ultimately encourage future health care leaders to build practices in the Jersey Shore area.”

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

- **Carrier Clinic - Staff Psychiatrist** (Belle Mead, NJ)
- **Consultation Liaison Psychiatrists**: Raritan Bay Medical Center (Perth Amboy)
- **Outpatient**: Ocean Medical Center (Brick, NJ)
- **Medical Director for Adult Inpatient Unit**: Riverview Medical Center (Red Bank, NJ)
- **Outpatient Child & Adolescent Psychiatrist**: Hackensack University Medical Center (Hackensack, NJ)
- **Geriatric Psychiatry**: Hackensack University Medical Center (Hackensack, NJ)
- **ED/Crisis Unit**: Jersey Shore University Medical Center (Neptune, NJ)
- **Telehealth Remote Psychiatrist - PT**

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Some benefits of working at SCF include no call, billing, coding and insurance issues handled by a separate department, 10 hours of administrative time per week, and no inpatient care.

For additional information, please contact: Kristen Smith (442)265-1606 kristensmith@co.imperial.ca.us
Tufts Medical Center Physicians Organization is an EEO/AA employer.

JOIN OUR TEAM | Clinical Director

Buffalo Psychiatric Center (BPC) is seeking an experienced Clinical Director (CD). The CD will serve as the Chief Medical Officer of BPC and is responsible for the administration, oversight, evaluation, and continuous improvement of all psychiatric, medical and contracted medical services provided by staff and consultants of the psychiatric center. This is an amazing opportunity for an experienced psychiatrist interested in making a difference in the recovery of a community of persons with significant mental health challenges through providing clinical leadership to a complex mental health organization and working closely with local and state level agency partners to make a positive impact on overall systems of mental health care and services delivery.

About Us:
For more than 135 years, Buffalo Psychiatric Center (BPC), has served the people of Western New York. We are located on a beautiful historic campus in the City of Buffalo. BPC is a 154-bed, NYS Office of Mental Health state-operated, Joint Commission accredited and CMS certified facility. BPC provides adult inpatient, outpatient, ACT, residential, vocational, and wellness services to individuals residing in Cattaraugus, Chautauqua, Erie and Niagara Counties.

Benefits Offered
• NYS Pension and retirement programs
• Comprehensive medical, dental and vision plans
• Flexible spending accounts for health and dependent care
• Generous paid time off: including vacations, holidays, personal days and sick leave
• Defense and Identification; broader in scope than typical malpractice coverage
• Academic affiliations with a number of prestigious institutions
• Salary Range: $244,212 - $283,241

Minimum Qualifications
To be considered, candidates must have:
• License and current registration to practice medicine in New York State or a New York State limited permit and licensure in another state or Canada, AND
• Certification in Psychiatry issued by the American Board of Psychiatry and Neurology (ABPN) or equivalent certifying body, AND
• Seven (7) years of experience providing services to people diagnosed with mental illness, of which two (2) years must have included supervising physicians and other clinical staff responsible for the delivery of treatment services; providing direction to staff regarding program objectives and the implementation of policy; and providing guidance to various clinical specialists.

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MISSOURI
physician practice of Tufts Medical Center, focused medical and psychiatric care along with person centered and strength based clinical and rehabilitative treatment. Applicants should be familiar with these evidence-based therapeutic procedures.

Tewksbury Hospital provides a therapeutic environment to provide patient focused medical and psychiatric care along with diagnostic services to meet the needs of patients with complex chronic psychological or social needs. Tewksbury Hospital is in the process of becoming the model facility for providing recovery oriented, trauma informed, family focused, person centered and strength based clinical and rehabilitative treatment.

There is no required on-call, no evenings, no weekends, no nights, or no holidays, although physicians can sign up for voluntary night and weekend shifts at additional pay. Attending Psychiatrists are eligible for a faculty appointment at Tufts at appropriate rank, a competitive salary and excellent benefits. As an employee of the Tufts Medical Center Physician’s Organization, the physician practice of Tufts Medical Center, you will receive a comprehensive benefits package, competitive compensation, and a generous employee retirement plan contribution.

Interested candidates, please send your CV and a letter of interest in confidence to:

Jennifer Colon
Physician Recruiter
Tufts Medical Center Physicians Organization
800 Washington Street, #1013
Boston, MA 02111
Telephone: 857-275-6126
Fax: 617-636-6366
Email: jcolon1@tuftsmedicalcenter.org
www.tuftsmedicalcenter.org

NEW JERSEY

CFG seeks an inpatient PSYCHIATRIST to work in beautiful, rural, Blackwood, NJ. Located within 30 minutes of Philadelphia, this hospital is located on serene country-like grounds. Offering a competitive salary, sign on bonus, and benefits package.

J1 and H1B Visa applicants welcome! REQUIREMENTS:
• A New Jersey psychiatry license or ability to obtain license
• Board certification within five (5) years of completing residency and must maintain certification. 
• Must possess good interpersonal communication and leadership skills.
• Must complete a satisfactory background investigation.

Contact: Karly Settle, ksettle@cfgpc.com, Ph: 856-938-8722
APPLY TODAY! https://cfgrfamilyguidance.com/careers/

NORTH CAROLINA

COASTAL NORTH CAROLINA – Seeking an energetic, compassionate, dedicated and self-motivated Psychiatrist to join our team providing outstanding, life changing psychiatric care. This Psychiatric center provides outpatient psychiatry, psychotherapy and psychological testing in a warm caring environment. In addition, the center staffs a medical team to provide inpatient services at two nearby freestanding psychiatric hospitals providing acute and residential treatment to children, teens and adults. Our team consists of 7 Psychiatrists, 4 Nurse Practitioners, 7 Psychiatric Physician Assistants, 6 Psychologists, and 9 Therapists. Offering a competitive compensation package & benefits. Position can be Outpatient, Inpatient, or a combination of both. The area provides a rich opportunity for outdoor enthusiasts. There are many lovely small towns along the intercoastal waterway nearby; and Wilmington is only an hour away and Raleigh is two and a half hours away. Please contact: Terry Good at terryg@horizonhealth.com; 304-684-5241. EOE

PSYCHIATRIST

Provide full-time face-to-face psychiatric services to patients in Raymore, MO for a minimum of 40 hours a week. In addition, may provide services to patients in Royal Oaks Hospital in Windsor, Missouri, as assigned. M.D. or professional equivalent degree, BC/BE in Psychiatry and Missouri medical license required. This position is eligible for the Employee Referral Program. Position is with Compass Health, Inc., d/b/a Pathways Community Health in Clinton, MO. Send C.V. to: Ms. Cathy Gregg, Director of Psychiatry Services at cgregg@phbc.org. Fax: 417-532-6606.

Pennsylvania

PSYCHIATRIST

AmeriCare Services is pleased to announce excellent full time opportunities with our group in Eastern and Western Pennsylvania. The positions are inpatient, Monday thru Friday with no on-call, weekend, evenings or holidays.

The compensation is $215.00 to $220.00 per hour. For confidential consideration call 610-695-8521 or email: KGallagher@AmerCareServices.com

Child & Adolescent Psychiatrist

Greenville, SC

Details Include:
• Candidate must be fellowship-trained and BC/BE in child and adolescent psychiatry
• Experience in an outpatient mental health setting, including telepsychiatry services
• Academic faculty position working with fellows, residents and medical students
• Competitive compensation
• Rich benefits package including relocation, malpractice, health and dental insurance
• OME allowance

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

Addiction Psychiatrist

Greenville, SC

Details Include:
• Experience in outpatient academic and community mental health settings
• Experience seeing patients with substance use disorder, co-occurring disorders and MAT
• Monday - Friday Outpatient with 1:10 weekend inpatient coverage
• Working with fellows, residents, medical students, and advanced practice providers
• Collaborative work with community partners including acute and residential rehab facilities.
• Competitive compensation
• Rich benefits package including relocation, malpractice, health and dental insurance
• OME allowance

Prisma Health is a not-for-profit health company and the largest healthcare system in South Carolina. With nearly 10,000 team members, 18 acute and specialty hospitals, 2,947 beds and more than 300 outpatient sites with nearly 2,000 physicians, Prisma Health serves more than 1.2 million unique patients annually in its 21-county market area that covers 50% of South Carolina. Prisma Health’s goal is to improve the health of all South Carolinians by enhancing clinical quality, the patient experience and access to affordable care, as well as conducting clinical research and training the next generation of medical professionals.

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

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

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

Prisma Health is an equal opportunity employer which proudly values diversity. Candidates of all backgrounds are encouraged to apply.
INGREZZA® (valbenazine) capsules is indicated for the treatment of adults with tardive dyskinesia.

**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 AND PRECAUTIONS**

**Somnolence**

INGREZZA can cause somnolence. Patients should not perform activities requiring mental alertness such as operating a motor vehicle or operating hazardous machinery until they know how they will be affected by INGREZZA.

**QT Prolongation**

INGREZZA may prolong the QT interval, although the degree of QT prolongation is not clinically significant at concentrations expected with recommended dosing. In patients taking a strong CYP2D6 or CYP3A4 inhibitor, or who are CYP2D6 poor metabolizers, INGREZZA concentrations may be higher and QT prolongation clinically significant. For patients who are CYP2D6 poor metabolizers or are taking a strong CYP2D6 inhibitor, dose reduction may be necessary. For patients taking a strong CYP3A4 inhibitor, reduce the dose of INGREZZA to 40 mg once daily. INGREZZA should be avoided in patients with congenital long QT syndrome or with arrhythmias associated with a prolonged QT interval. For patients at increased risk of a prolonged QT interval, assess the QT interval before increasing the dosage.

**Parkinsonism**

INGREZZA may cause parkinsonism in patients with tardive dyskinesia. Parkinsonism has also been observed with other MAO type B inhibitors. In 5 placebo-controlled clinical studies in patients with tardive dyskinesia, the incidence of parkinson-like adverse events was 3% of patients treated with INGREZZA and <1% of placebo-treated patients. Postmarketing safety reports have described parkinson-like symptoms, some of which were severe and required hospitalization. In most cases, severe parkinsonism occurred within the first 2 weeks after starting or increasing the dose of INGREZZA. Associated symptoms have included falls, gait disturbances, tremor, drooling, and hypokinesia. In cases in which follow-up clinical information was available, parkinson-like symptoms were reported to resolve following discontinuation of INGREZZA therapy. Reduce the dose or discontinue INGREZZA treatment in patients who develop clinically significant parkinson-like signs or symptoms.

**ADVERSE REACTIONS**

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

- Hypersensitivity
- Somnolence
- QT Prolongation
- Parkinsonism

**Clinical Trials Experience**

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

**Variable and Fixed Dose Placebo-Controlled Trial Experience**

The safety of INGREZZA was evaluated in 3 placebo-controlled studies, each 6 weeks in duration (fixed dose, dose escalation, dose reduction), including 445 patients. Patients were 26 to 84 years of age with moderate to severe tardive dyskinesia and had concurrent diagnoses of mood disorder (27%) or schizophrenia (22%). The mean age was 56 years. Patients were 57% Caucasian, 39% African-American, and 4% other. With respect to ethnicity, 26% were Hispanic or Latin. All subjects continued previous stable regimens of antipsychotics; 85% and 27% of subjects, respectively, were taking atypical and typical antipsychotics. Patients were treated at a stable dose for a minimum of 1 year unless the investigator determined that changes in regimen were necessary.

**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>
<thead>
<tr>
<th>Adverse Reaction1</th>
<th>INGREZZA (n=262) (%)</th>
<th>Placebo (n=189) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence (somnolence, fatigue, sedation)</td>
<td>10.9%</td>
<td>4.2%</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Artichoke-like effects (dry mouth, constipation, disturbance in attention, vision blurred, urinary retention)</strong></td>
<td>5.4%</td>
<td>4.9%</td>
</tr>
<tr>
<td><strong>Balance disorders (fall, gait disturbance, dizziness, balance disorder)</strong></td>
<td>4.1%</td>
<td>2.2%</td>
</tr>
<tr>
<td><strong>Headache</strong></td>
<td>3.4%</td>
<td>2.7%</td>
</tr>
<tr>
<td><strong>Arthralgia (arthralgia, stiffness)</strong></td>
<td>2.7%</td>
<td>0.5%</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vomiting</strong></td>
<td>2.6%</td>
<td>0.6%</td>
</tr>
<tr>
<td><strong>Nausea</strong></td>
<td>2.3%</td>
<td>2.1%</td>
</tr>
<tr>
<td><strong>Musculoskeletal Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Arthralgia</strong></td>
<td>2.3%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

*Within each adverse reaction category, the observed adverse reactions are listed in order of decreasing frequency.*

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

**Endocrine Disorders:** blood glucose increased

**General Disorders:** weight increased

**Infectious Disorders:** respiratory infections

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

**Psychiatric Disorders:** anxiety, insomnia

During controlled trials, there was a dose-related increase in prolactin. Additionally, there was a dose-related increase in alkaline phosphatase and bilirubin, suggesting a potential risk for cholestasis.

**Postmarketing Experience**

The following adverse reactions have been identified during post-approval use of INGREZZA that are not included in other sections of the labeling. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

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

**Skin and Subcutaneous Tissue Disorders:** rash

**DRUG INTERACTIONS**

**Dogs Having Clinically Important Interactions with INGREZZA**

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

*The induction potency of St. John's wort may vary widely based on preparation.*

**Monoamine Oxidase Inhibitors (MAOIs)**

Clinical Implication:

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

**Prevention or Management:**

Avoid concomitant use of INGREZZA with MAOIs.

**Examples:**

Isocarboxazid, phenelzine, selegiline

**Strong CYP3A4 Inhibitors**

Clinical Implication:

Concomitant use of INGREZZA with strong CYP3A4 inhibitors increased the exposure of 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:**

Fenova, ketonazoline, clarithromycin

**Strong CYP2D6 Inhibitors**

Clinical Implication:

Concomitant use of INGREZZA with strong CYP2D6 inhibitors increased the exposure of 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 CYP2D6 inhibitor.

**Examples:**

Paroxetine, fluoxetine, quinidine

**Strong CYP3A4 Inducers**

Clinical Implication:

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

**Prevention or Management:**

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

**Examples:**

Rifampin, carbamazepine, phenobarbital, 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.

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

Dosage adjustment for INGREZZA is not necessary when used in combination with substrates of CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5 based on in vitro study results.

**OVERDOSAGE**

**Human Experience**

The pre-marketing clinical trials involving INGREZZA in approximately 850 subjects do not provide information regarding symptoms with overdose.

**Management of Overdose**

No specific antidotes for INGREZZA are known. In managing overdose, provide supportive care, including close medical supervision and monitoring, and consider the possibility of multiple drug involvement. If an overdose occurs, consult a certified Poison Control Center (1-800-222-1222 or www.poisong.org).

For further information on INGREZZA, call 84-INGREZZA (844-647-3992).

**Distributed by:**

Neurocrine Biosciences, Inc.
San Diego, CA 92130

INGREZZA is a registered trademark of Neurocrine Biosciences, Inc.
CP-928-US-0239v5 05/2020
Important Information

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

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

WARNINGS & PRECAUTIONS
Somnolence
INGREZZA can cause somnolence. Patients should not perform activities requiring mental alertness such as operating a motor vehicle or operating hazardous machinery until they know how they will be affected by INGREZZA.

QT Prolongation
INGREZZA may prolong the QT interval, although the degree of QT prolongation is not clinically significant at concentrations expected with recommended dosing. INGREZZA should be avoided in patients with congenital long QT syndrome or with arrhythmias associated with a prolonged QT interval. For patients at increased risk of a prolonged QT interval, assess the QT interval before increasing the dosage.

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

ADVERSE REACTIONS
The most common adverse reaction (≥5% and twice the rate of placebo) is somnolence. Other adverse reactions (≥2% and >Placebo) include: anticholinergic effects, balance disorders, falls, headache, akathisia, vomiting, nausea, and arthralgia.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit MedWatch at www.fda.gov/medwatch or call 1-800-FDA-1088.

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

The duloxetine your patients require—approved in a sprinkle formulation designed for those who cannot or will not swallow solid forms of medication

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

Dosing and Administration

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

IMPORTANT SAFETY INFORMATION (cont’d)

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

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

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

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

Please see additional Important Safety Information throughout this journal cover wrap, and Brief Summary of Full Prescribing Information, including Boxed Warning.
Prescribe the Only Formulation of Duloxetine That is Designed to Be Opened and Sprinkled
drizalma Sprinkle™ is designed for patients who cannot or will not swallow solid medication forms

Drizalma Sprinkle™ provides effective therapy in one formulation for 4 different indications:
- Major Depressive Disorder (MDD) in adults
- Generalized Anxiety Disorder (GAD) in adults and pediatric patients aged 7 to 17 years
- Diabetic Peripheral Neuropathic Pain (DPNP) in adults
- Chronic musculoskeletal pain in adults

IMPORTANT SAFETY INFORMATION (cont’d)
USE IN SPECIFIC POPULATIONS (cont’d)
- Lactation: Advise breastfeeding women using duloxetine to monitor infants for sedation, poor feeding and poor weight gain and to seek medical care if they notice these signs

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

Please see additional Important Safety Information throughout this journal cover wrap, and Brief Summary of Full Prescribing Information, including Boxed Warning.

To Learn More, Visit: drizalmasprinklehcp.com


This promotional program was developed in conjunction with and sponsored by Sun Pharmaceutical Industries, Inc.
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BENEFITS OF ATTENDING

• Learn about state-of-the-art treatments in major depressive disorder
• Hear a debate-style presentation featuring 2 experts, each offering opposing viewpoints regarding the use of antidepressants to treat bipolar disorder, and weigh in on who you think has the most persuasive arguments!
• Expand your skill set regarding strategies for self-care and creating resilience
• Learn about the psychiatric complications of COVID-19 and psychiatry in a postpandemic world
• Discover emerging research on the use of cannabis for psychiatric indications
• Explore cultural challenges in psychiatry

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<tr>
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<tr>
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<td>Fellows*</td>
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<tr>
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<tr>
<td>Industry**</td>
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<td>$599</td>
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By attending this Physicians’ Education Resource® LLC program, you agree to abide by and engage in certain health- and safety-beneficial conduct while attending the event, including providing proof at check-in of being 2 weeks removed from receiving a full COVID-19 vaccination or results from a negative COVID-19 viral test taken no more than 3 days before the program. For information on the specific safety precautions that will be in place, please visit event.gotoper.com/psych2021 and click on Health & Safety Precautions.
Annual Psychiatric Times™
WORLD CME CONFERENCE™

LIVE IN-PERSON AND VIRTUALLY ON SEPT. 30 – OCT. 2, 2021

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HOT TOPICS FOR 2021

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• Wellness for our patients and for ourselves
• How to teach neuroscience
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