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Is Video Game Addiction a

DISORDER?

» Rashmi Parmar, MD, and Julian Lagoy, MD

In Ohio, a 17-year-old boy shot both of his parents, killing his mother, because they took away his Halo 3 video game. His defense was that he was pushed to the brink by his addiction to video games, often playing for 18 hours straight.¹

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COMMENTARY

Psychiatry in the Year 2500: Lessons Learned From History

» Joel Yager, MD

For the past decade, I have taught 6-hour annual seminars on the history of psychiatry to psychiatric residents. This course was assigned to me, in part, because I have lived through the history of

psychiatry for more than 50 years. Through this seminar, my residents and I have come to realize that each generation's members, ourselves included, look back on earlier psychiatric concepts and practices, from the ancients right through recent times, with a mixture of

bemusement, pity, and horror. Our bemusement and pity stem from previous eras' well-intentioned but quaint or misguided ideas based on scientific ignorance, whereas our horror is evoked by seemingly inhumane practices inflicted on psychiatrically vulnerable populations.¹

Assuming humans survive and continue doing competent science, we can imagine psychiatrists of the year 2500, enjoying knowledge far more advanced than ours, and reacting to our ideas and practices, too, with bemusement, pity, and horror. From this viewpoint, let us try to envision the history of future psychiatry, to not only

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#1 PRESCRIBED ONCE-MONTHLY LONG-ACTING INJECTABLE ATYPICAL ANTIPSYCHOTIC¹

 **INVEGA SUSTENNA[®]**
paliperidone palmitate extended-release
injectable suspension

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^{2*}

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 trial³



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

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

Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status including delirium, and autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (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 and in patients with risk factors for prolonged QTc interval. Paliperidone should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias. Certain circumstances may increase the risk of the occurrence of torsades de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval.

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

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

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

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

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

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

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

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

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

initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

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

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

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

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

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

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

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

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

Commonly Observed Adverse Reactions for INVEGA SUSTENNA®: The most common adverse reactions in clinical trials in patients with schizophrenia (≥5% and twice placebo) were injection site reactions, somnolence/sedation, dizziness, akathisia and extrapyramidal disorder.

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 (LRx) and Medical Claims (Dx) in schizophrenia in adults; April 2020–March 2021.
2. Schreiner A, Adamsoo K, Altamura AC, et al. Paliperidone palmitate versus oral antipsychotics in recently diagnosed schizophrenia. *Schizophr Res*. 2015;169(1-3):393-399.
3. INVEGA SUSTENNA® [Prescribing Information]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; February 2021.



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

In a long-term open-label pharmacokinetic and safety study in subjects with schizophrenia in which the highest dose available (234 mg) was evaluated, the mean changes from baseline in lipid values are presented in Table 3.

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

	INVEGA SUSTENNA® 234 mg	
	Week 29	Week 53
	Mean change from baseline (mg/dL)	
Cholesterol	n=112	n=100
Change from baseline	-1.2	0.1
LDL	n=107	n=89
Change from baseline	-2.7	-2.3
HDL	n=112	n=98
Change from baseline	-0.8	-2.6
Triglycerides	n=112	n=100
Change from baseline	16.2	37.4

The mean changes from baseline in lipid values during the initial 25-week open-label period and at the endpoint of the subsequent 15-month double-blind period in a long-term study in subjects with schizoaffective disorder are presented in Table 4.

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

	Open-Label Period		Double-Blind Period	
	INVEGA SUSTENNA®		Placebo	INVEGA SUSTENNA®
	Mean change from baseline (mg/dL)			
Cholesterol	n=198	n=119	n=132	
Change from baseline	-3.9	-4.2	2.3	
LDL	n=198	n=117	n=130	
Change from baseline	-2.7	-2.8	5.9	
HDL	n=198	n=119	n=131	
Change from baseline	-2.7	-0.9	-0.7	
Triglycerides	n=198	n=119	n=132	
Change from baseline	7.0	2.5	-12.3	

Weight Gain

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

Table 5: Mean Change in Body Weight (kg) and the Proportion of Subjects with $\geq 7\%$ Gain in Body Weight from Four Placebo-Controlled, 9- to 13-Week, Fixed-Dose Studies in Subjects with Schizophrenia

	Placebo	INVEGA SUSTENNA®					
		39 mg	78 mg	156 mg	234/39 mg ^a	234/156 mg ^a	234/234 mg ^a
Weight (kg) Change from baseline	n=451	n=116	n=280	n=267	n=137	n=144	n=145
	-0.4	0.4	0.8	1.4	0.4	0.7	1.4
Weight Gain $\geq 7\%$ increase from baseline	3.3%	6.0%	8.9%	9.0%	5.8%	8.3%	13.1%

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

In a long-term open-label pharmacokinetic and safety study in which the highest dose available (234 mg) was evaluated, INVEGA SUSTENNA® was associated with a mean change in weight of +2.4 kg at Week 29 (n=134) and +4.3 kg at Week 53 (n=113).

During the initial 25-week open-label period of a long-term study in subjects with schizoaffective disorder, INVEGA SUSTENNA® was associated with a mean change in weight of +2.2 kg and 18.4% of subjects had an increase in body weight of $\geq 7\%$ (n=653). At the endpoint of the subsequent 15-month double-blind period of the study, INVEGA SUSTENNA® was associated with a mean change in weight of -0.2 kg and 13.0% of subjects had an increase in body weight of $\geq 7\%$ (n=161); the placebo group had a mean change in weight of -0.8 kg and 6.0% of subjects had an increase in body weight of $\geq 7\%$ (n=168).

Orthostatic Hypotension and Syncope

Paliperidone can induce orthostatic hypotension and syncope in some patients because of its alpha-adrenergic blocking activity. Syncope was reported in $< 1\%$ (4/1293) of subjects treated with INVEGA SUSTENNA® in the recommended dose range of 39 mg to 234 mg in the four fixed-dose, double-blind, placebo-controlled trials compared with 0% (0/510) of subjects treated with placebo. In the four fixed-dose efficacy studies in subjects with schizophrenia, orthostatic hypotension was reported as an adverse event by $< 1\%$ (2/1293) of INVEGA SUSTENNA®-treated subjects compared to 0% (0/510) with placebo. Incidences of orthostatic hypotension and syncope in the long-term studies in subjects with schizophrenia and schizoaffective disorder were similar to those observed in the short-term studies.

INVEGA SUSTENNA® should be used with caution in patients with known cardiovascular disease (e.g., heart failure, history of myocardial infarction or ischemia, conduction abnormalities), cerebrovascular disease, or conditions that predispose the patient to hypotension (e.g., dehydration, hypovolemia, and treatment with antihypertensive medications). Monitoring of orthostatic vital signs should be considered in patients who are vulnerable to hypotension.

Falls

Somnolence, postural hypotension, motor and sensory instability have been reported with the use of antipsychotics, including INVEGA SUSTENNA®, which may lead to falls and, consequently, fractures or other fall-related injuries. For patients, particularly the elderly, with diseases, conditions, or medications that 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

In clinical trial and/or postmarketing experience, events of leukopenia and neutropenia have been reported temporally related to antipsychotic agents, including INVEGA SUSTENNA®. Agranulocytosis has also been reported.

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

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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 $< 1000/\text{mm}^3$) and follow their WBC until recovery.

Hyperprolactinemia

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

Hyperprolactinemia, regardless of etiology, may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotrophin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects.

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is considered in a patient with previously detected breast cancer. An increase in the incidence of pituitary gland, mammary gland, and pancreatic islet cell neoplasia (mammary adenocarcinomas, pituitary and pancreatic adenomas) was observed in the risperidone carcinogenicity studies conducted in mice and rats [see *Nonclinical Toxicology* (13.1) in Full Prescribing Information]. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans, but the available evidence is too limited to be conclusive.

Prolactin data from two long-term, double-blind, placebo-controlled studies with INVEGA SUSTENNA® are presented below; one study was in a population of patients with schizophrenia; the second study was in patients with schizoaffective disorder.

Schizophrenia

In a long-term maintenance trial of INVEGA SUSTENNA® in schizophrenia patients (Study PSY-3001), see *Clinical Studies* (14.1), elevations of prolactin to above the reference range (> 18 ng/mL in males and > 30 ng/mL in females) relative to open-label baseline at any time during the double-blind phase were noted in a higher percentage of the patients in the INVEGA SUSTENNA® group than those in the placebo group in males (51.9% vs. 29.0%) and in females (50.5% vs. 42.9%). During the double-blind phase, 4 females (4.2%) in the INVEGA SUSTENNA® group experienced potentially prolactin-related adverse reactions (amenorrhea N=2; galactorrhea N=1; menstruation irregular N=1), while 2 females (2.2%) in the placebo group experienced potentially prolactin-related adverse reactions (amenorrhea N=1; breast pain N=1). One male (0.9%) in the INVEGA SUSTENNA® group experienced erectile dysfunction and 1 male (0.9%) in placebo group experienced gynecomastia.

Prior to the double-blind phase (during the 33-week open-label phase of the long-term maintenance trial), the mean (SD) serum prolactin values at baseline were 14.9 (22.3) ng/mL in males (N=490) and 35.2 (39.6) ng/mL in females (N=358). At the end of the open-label phase, mean (SD) prolactin values were 24.7 (22.5) ng/mL in males (N=470) and 59.5 (38.1) ng/mL in females (N=333). During the open-label phases 49.2% 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 compared to males (5.3% vs. 1.8%). Amenorrhea (2.5%) in females and no single potentially prolactin-related adverse reaction in males were observed with a rate greater than 2%.

Schizoaffective Disorder

In a long-term maintenance trial of INVEGA SUSTENNA® in patients with schizoaffective disorder (Study SCA-3004) see *Clinical Studies* (14.2), elevations of prolactin to above the reference range (> 13.13 ng/mL in males and > 26.72 ng/mL in females) relative to open-label baseline at any time during the 15-month double-blind phase were noted in a higher percentage of patients in the INVEGA SUSTENNA® group than those in the placebo group in males (55.6% vs. 23.2%) and in females (44.3% vs. 25.0%). During the 15-month double-blind phase, 11 females (13.9%) in the INVEGA SUSTENNA® group had 14 potentially prolactin-related adverse reactions (hyperprolactinemia N=3; blood prolactin increased N=4; libido decreased N=1; amenorrhea N=3; galactorrhea N=3), while 5 females (5.8%) in the placebo group had 6 potentially prolactin-related adverse reactions (hyperprolactinemia N=2; blood prolactin increased N=1; amenorrhea N=2; galactorrhea N=1). Six males (7.1%) in the INVEGA SUSTENNA® group experienced 6 potentially prolactin-related adverse reactions (hyperprolactinemia N=4; libido decreased N=1; erectile dysfunction N=1), while 1 male (1.2%) 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 (14.0) ng/mL in males (N=352) and 39.1 (44.6) ng/mL in females (N=302). At the end of the open-label phase, mean (SD) prolactin values were 32.8 (17.2) ng/mL in males (N=275) and 72.4 (46.5) ng/mL in females (N=239). During the open-label phase, 48.9% of females and 53.3% 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 compared to males (10.0% vs. 9.0%). Amenorrhea (5.8%) and galactorrhea (2.9%) in females and libido decrease (2.8%) and erectile dysfunction (2.5%) 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® [see *Adverse Reactions*]. Antipsychotics, including INVEGA SUSTENNA®, have the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that paliperidone therapy does not adversely affect them.

Seizures

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

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

Dysphagia

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.

Priapism

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

Disruption of Body Temperature Regulation

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

ADVERSE REACTIONS

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

- Increased mortality in elderly patients with dementia-related psychosis [see *Boxed Warning and Warnings and Precautions*]
- Cerebrovascular adverse reactions, including stroke, in elderly patients with dementia-related psychosis [see *Warnings and Precautions*]
- Neuroleptic malignant syndrome [see *Warnings and Precautions*]

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- 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]
- Priapism [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 3817 subjects (approximately 1705 patient-years exposure) with schizophrenia who received at least one dose of INVEGA SUSTENNA® in the recommended dose range of 39 mg to 234 mg and a total of 510 subjects with schizophrenia who received placebo. Among the 3817 INVEGA SUSTENNA®-treated subjects, 1293 received INVEGA SUSTENNA® in four fixed-dose, double-blind, placebo-controlled trials (one 9-week and three 13-week studies), 849 received INVEGA SUSTENNA® in the maintenance trial (median exposure 229 days during the initial 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 13-week studies included a 234 mg INVEGA SUSTENNA® initiation dose followed by treatment with either 39 mg, 156 mg, or 234 mg every 4 weeks.

The safety of INVEGA SUSTENNA® was also evaluated in a 15-month, long-term study comparing INVEGA SUSTENNA® to selected oral antipsychotic therapies in adult subjects with schizophrenia. A total of 226 subjects received INVEGA SUSTENNA® during the 15-month, open-label period of this study; 218 subjects received selected oral antipsychotic therapies. The safety of INVEGA SUSTENNA® was similar to that seen in previous double-blind, placebo-controlled clinical trials in adult subjects with schizophrenia. The safety of INVEGA SUSTENNA® was also evaluated in a long-term study in adult subjects with schizoaffective disorder. A total of 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: The most common (at least 5% in any INVEGA SUSTENNA® group) and likely drug-related (adverse events for which the drug rate is at least twice the placebo rate) adverse reactions from the double-blind, placebo-controlled trials in subjects with schizophrenia were injection site reactions, somnolence/sedation, dizziness, akathisia, and extrapyramidal disorder. No occurrences of adverse events reached this threshold in the long-term double-blind, placebo-controlled study in subjects with schizoaffective disorder.

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

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

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

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

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

System Organ Class Adverse Reactions	Placebo ^a (N=510)	INVEGA SUSTENNA®					
		39 mg (N=130)	78 mg (N=302)	156 mg (N=312)	234/39 mg ^b (N=160)	234/156 mg ^b (N=165)	234/234 mg ^b (N=163)
Total percentage of subjects with adverse reactions	70	75	68	69	63	60	63
Gastrointestinal disorders							
Abdominal discomfort/abdominal pain upper	2	2	4	4	1	2	4
Diarrhea	2	0	3	2	1	2	2
Dry mouth	1	3	1	0	1	1	1
Nausea	3	4	4	3	2	2	2
Toothache	1	1	1	3	1	2	3
Vomiting	4	5	4	2	3	2	2
General disorders and administration site conditions							
Asthenia	0	2	1	<1	0	1	1
Fatigue	1	1	2	2	1	2	1
Injection site reactions	2	0	4	6	9	7	10
Infections and infestations							
Nasopharyngitis	2	0	2	2	4	2	2
Upper respiratory tract infection	2	2	2	2	1	2	4
Urinary tract infection	1	0	1	<1	1	1	2
Investigations							
Weight increased	1	4	4	1	1	1	2

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

System Organ Class Adverse Reactions	Placebo ^a (N=510)	INVEGA SUSTENNA®					
		39 mg (N=130)	78 mg (N=302)	156 mg (N=312)	234/39 mg ^b (N=160)	234/156 mg ^b (N=165)	234/234 mg ^b (N=163)
Musculoskeletal and connective tissue disorders							
Back pain	2	2	1	3	1	1	1
Musculoskeletal stiffness	1	1	<1	<1	1	1	2
Myalgia	1	2	1	<1	1	0	2
Pain in extremity	1	0	2	2	2	3	0
Nervous system disorders							
Akathisia	3	2	2	3	1	5	6
Dizziness	1	6	2	4	1	4	2
Extrapyramidal disorder	1	5	2	3	1	0	0
Headache	12	11	11	15	11	7	6
Somnolence/sedation	3	5	7	4	1	5	5
Psychiatric disorders							
Agitation	7	10	5	9	8	5	4
Anxiety	7	8	5	3	5	6	6
Nightmare	<1	2	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders							
Cough	1	2	3	1	0	1	1
Vascular disorders							
Hypertension	1	2	1	1	1	1	0

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

^a Placebo group is pooled from all studies and included either deltoid or gluteal injection depending on study design.

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

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

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) for which a drug 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, oculogyric crisis, vision blurred

Gastrointestinal disorders: constipation, dyspepsia, flatulence, salivary hypersecretion

Immune system disorders: hypersensitivity

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

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

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

Nervous system disorders: bradykinesia, cerebrovascular accident, cogwheel rigidity, convulsion, dizziness postural, drooling, dysarthria, dyskinesia, dystonia, hypertonia, lethargy, oromandibular dystonia, parkinsonism, psychomotor hyperactivity, syncope

Psychiatric disorders: insomnia, libido decreased, restlessness

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

Respiratory, thoracic and mediastinal disorders: nasal congestion

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

Demographic Differences

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

Extrapyramidal Symptoms (EPS)

Pooled data from the two double-blind, placebo-controlled, 13-week, fixed-dose trials in adult subjects with schizophrenia provided information regarding EPS. Several methods were used to measure EPS: (1) the Simpson-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) Assessed by Incidence of Rating Scales and Use of Anticholinergic Medication – Schizophrenia Studies in Adults

Scale	Percentage of Subjects			
	Placebo (N=262)	39 mg (N=130)	78 mg (N=223)	156 mg (N=228)
Parkinsonism ^a	9	12	10	6
Akathisia ^b	5	5	6	5
Dyskinesia ^c	3	4	6	4
Use of Anticholinergic Medications ^d	12	10	12	11

^a For parkinsonism, percent of subjects with Simpson-Angus Total score > 0.3 at endpoint (Total score defined as total sum of items score divided by the number of items)

^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 ≥ 3 on any of the first 7 items or a score ≥ 2 on two or more of any of the first 7 items of the Abnormal Involuntary Movement Scale at endpoint

^d Percent of subjects who received anticholinergic medications to treat EPS

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Table 8: Extrapyramidal Symptoms (EPS)-Related Events by MedDRA Preferred Term – Schizophrenia Studies in Adults

EPS Group	Percentage of Subjects			
	Placebo (N=262)	INVEGA SUSTENNA® 39 mg (N=130)	78 mg (N=223)	156 mg (N=228)
Overall percentage of subjects with EPS-related adverse events	10	12	11	11
Parkinsonism	5	6	6	4
Hyperkinesia	2	2	2	4
Tremor	3	2	2	3
Dyskinesia	1	2	3	1
Dystonia	0	1	1	2

Parkinsonism group includes: Extrapyramidal disorder, hypertonia, musculoskeletal stiffness, parkinsonism, drooling, masked facies, muscle tightness, hypokinesia
Hyperkinesia group includes: Akathisia, restless legs syndrome, restlessness
Dyskinesia group includes: Dyskinesia, choreoathetosis, muscle twitching, myoclonus, tardive dyskinesia
Dystonia group includes: Dystonia, muscle spasms

The results across all phases of the maintenance trial in subjects with schizophrenia exhibited comparable findings. In the 9-week, fixed-dose, double-blind, placebo-controlled trial, the proportions of parkinsonism and akathisia assessed by incidence of rating scales were higher in the INVEGA SUSTENNA® 156 mg group (18% and 11%, respectively) than in the INVEGA SUSTENNA® 78 mg group (9% and 5%, respectively) and placebo group (7% and 4%, respectively).

In the 13-week study in subjects with schizophrenia involving 234 mg initiation dosing, the incidence of any EPS was similar to that of the placebo group (8%), but exhibited a dose-related pattern with 6%, 10%, and 11% in the INVEGA SUSTENNA® 234/39 mg, 234/156 mg, and 234/234 mg groups, respectively. Hyperkinesia was the most frequent category of EPS-related adverse events in this study, and was reported at a similar rate between the placebo (4.9%) and INVEGA SUSTENNA® 234/156 mg (4.8%) and 234/234 mg (5.5%) groups, but at a lower rate in the 234/39 mg group (1.3%).

In the long-term study in subjects with schizoaffective disorder, EPS reported during the 25-week open-label INVEGA SUSTENNA® treatment included hyperkinesia (12.3%), parkinsonism (8.7%), tremor (3.4%), dyskinesia (2.5%), and dystonia (2.1%). During the 15-month double-blind treatment, the incidence of any EPS was similar to that of the placebo group (8.5% and 7.1% respectively). The most commonly reported treatment-emergent EPS-related adverse events (>2%) in any treatment group in the double-blind phase of the study (INVEGA SUSTENNA® versus placebo) were hyperkinesia (3.7% vs. 2.9%), parkinsonism (3.0% vs. 1.8%), and tremor (1.2% vs. 2.4%).

Dystonia

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

Pain Assessment and Local Injection Site Reactions

In the pooled data from the two 13-week, fixed-dose, double-blind, placebo-controlled trials in subjects with schizophrenia, 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 9.8; 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.

In the 13-week study involving 234 mg initiation dosing in subjects with schizophrenia, occurrences of induration, redness, or swelling, as assessed by blinded study personnel, were infrequent, generally mild, decreased over time, and similar in incidence between the INVEGA SUSTENNA® and placebo groups. Investigator ratings of injection pain were similar for the placebo and INVEGA SUSTENNA® groups. Investigator evaluations of the injection site after the first injection for redness, swelling, induration, and pain were rated as absent for 69-100% of subjects in both the INVEGA SUSTENNA® and placebo groups. At Day 92, investigators rated absence of redness, swelling, induration, and pain in 95-100% of subjects in both the INVEGA SUSTENNA® and placebo groups.

Additional Adverse Reactions Reported in Clinical Trials with Oral Paliperidone

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

Cardiac disorders: bundle branch block left, sinus arrhythmia

Gastrointestinal disorders: abdominal pain, small intestinal obstruction

General disorders and administration site conditions: edema, edema peripheral

Immune system disorders: anaphylactic reaction

Infections and infestations: rhinitis

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

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

Psychiatric disorders: sleep disorder

Reproductive system and breast disorders: breast engorgement

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

Skin and subcutaneous tissue disorders: rash papular

Vascular disorders: hypotension, ischemia

Postmarketing Experience

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

Cases of anaphylactic reaction after injection with INVEGA SUSTENNA® have been reported during postmarketing experience in patients who have previously tolerated oral risperidone or oral paliperidone.

Paliperidone is the major active metabolite of risperidone. Adverse reactions reported with oral risperidone and risperidone long-acting injection can be found in the *Adverse Reactions* sections of the package inserts for those products.

DRUG INTERACTIONS

Drugs Having Clinically Important Interactions with INVEGA SUSTENNA®

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

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Table 9. Clinically Important Drug Interactions with INVEGA SUSTENNA®

Concomitant Drug Name or Drug Class	Clinical Rationale	Clinical Recommendation
Centrally Acting Drugs and Alcohol	Given the primary CNS effects of paliperidone, concomitant use of centrally acting drugs and alcohol may modulate the CNS effects of INVEGA SUSTENNA®.	INVEGA SUSTENNA® should be used with caution in combination with other centrally acting drugs and alcohol [see <i>Adverse Reactions</i>].
Drugs with Potential for Inducing Orthostatic Hypotension	Because INVEGA SUSTENNA® has the potential for inducing orthostatic hypotension, an additive effect may occur when INVEGA SUSTENNA® is administered with other therapeutic agents that have this potential [see <i>Warnings and Precautions</i>].	Monitor orthostatic vital signs in patients who are vulnerable to hypotension [see <i>Warnings and Precautions</i>].
Strong Inducers of CYP3A4 and P-gp (e.g., carbamazepine, rifampin, or St. John's Wort)	The concomitant use of paliperidone and strong inducers of CYP3A4 and P-gp may decrease the exposure of paliperidone [see <i>Clinical Pharmacology</i> (12.3) in <i>Full Prescribing Information</i>].	Avoid using CYP3A4 and/or P-gp inducers with INVEGA SUSTENNA® during the 1-month dosing interval, if possible. If administering a strong inducer is necessary, consider managing the patient using paliperidone extended-release tablets [see <i>Dosage and Administration</i> (2.5) in <i>Full Prescribing Information</i>].
Levodopa and Other Dopamine Agonists	Paliperidone may antagonize the effect of levodopa and other dopamine agonists.	Monitor and manage patient as clinically appropriate.

Drugs Having No Clinically Important Interactions with INVEGA SUSTENNA®

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

Pharmacokinetic interaction between lithium and INVEGA SUSTENNA® is also unlikely.

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to atypical antipsychotics, including INVEGA SUSTENNA®, during pregnancy. Healthcare providers are encouraged to register patients by contacting the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or online at <http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/>.

Risk Summary

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

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

In animal reproduction studies, there were no treatment related effects on the offspring when pregnant rats were injected intramuscularly with paliperidone palmitate during the period of organogenesis at doses up to 10 times the maximum recommended human dose (MRHD) of 234 mg paliperidone based on mg/m² body surface area. There were no increases in fetal abnormalities when pregnant rats and rabbits were treated orally with paliperidone during the period of organogenesis with up to 8 times the MRHD of 12 mg of paliperidone based on mg/m² body surface area. Additional reproduction toxicity studies were conducted with orally administered risperidone, which is extensively converted to paliperidone (see *Animal data*).

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

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

Fetal/Neonatal Adverse Reactions

Extrapyramidal and/or withdrawal symptoms, including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder have been reported in neonates who were exposed to antipsychotic drugs, including INVEGA SUSTENNA®, during the third trimester of pregnancy. These symptoms have varied in severity. Monitor neonates exhibiting extrapyramidal and/or withdrawal symptoms and manage symptoms appropriately. Some neonates recovered within hours or days without specific treatment; others required prolonged hospitalization.

Data

Human Data

Published data from observational studies, birth registries, and case reports on the use of atypical antipsychotics during pregnancy do not report a clear association with antipsychotics and major birth defects. A prospective observational study including 6 women treated with risperidone, the parent compound of paliperidone, demonstrated placental passage of risperidone and paliperidone. A retrospective cohort study from a Medicaid database of 9258 women exposed to antipsychotics during pregnancy did not indicate an overall increased risk for major birth defects. There was a small increase in the risk of major birth defects (RR= 1.26, 95% CI 1.02-1.56) and of cardiac malformations (RR=1.26, 95% CI 0.88-1.81) in a subgroup of 1566 women exposed to the parent compound of paliperidone, risperidone, during the first trimester of pregnancy; however, there is no mechanism of action to explain the difference in malformation rates.

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Animal Data

There were no treatment-related effects on the offspring when pregnant rats were injected intramuscularly with paliperidone palmitate extended-release injectable suspension during the period of organogenesis at doses up to 250 mg/kg, which is 10 times MRHD of 234 mg paliperidone based on mg/m² body surface area.

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

Additional reproduction toxicity studies were conducted with orally administered risperidone, which is extensively converted to paliperidone. Cleft palate was observed in the offspring of pregnant mice treated with risperidone at 3 to 4 times the MRHD of 16 mg based on mg/m² body surface area; maternal toxicity occurred at 4 times the MRHD. There was no evidence of teratogenicity in embryo-fetal developmental toxicity studies with risperidone in rats and rabbits at doses up to 6 times the MRHD of 16 mg/day risperidone based on mg/m² body surface area. When the offspring of pregnant rats, treated with risperidone at 0.6 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 0.5 to 1.2 times the MRHD; the postnatal development and growth of the offspring was delayed.

In rat reproduction studies with risperidone, pup deaths occurred at oral doses which are less than the MRHD of risperidone based on 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 RISPEDAL® package insert).

Lactation

Risk Summary

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

Clinical Considerations

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

Females and Males of Reproductive Potential

Infertility

Females

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

Pediatric Use

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

Juvenile Animal Studies

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

Juvenile dogs were treated for 40 weeks with oral risperidone, which is extensively metabolized to paliperidone in animals and humans, at doses of 0.31, 1.25, or 5 mg/kg/day. Decreased bone length and density were seen with a no-effect dose of 0.31 mg/kg/day, which produced plasma levels (AUC) of risperidone plus paliperidone 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 males and females. The above effects showed little or no reversibility in females after a 12-week drug-free recovery period.

The long-term effects of INVEGA SUSTENNA® on growth and sexual maturation have not been fully evaluated in children and adolescents.

Geriatric Use

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

This drug is known to be substantially excreted by the kidney and clearance is decreased in patients with renal impairment [*see Clinical Pharmacology (12.3) in Full Prescribing Information*], who should be given reduced doses. Because elderly patients are more likely to have decreased renal function, adjust dose based on renal function [*see Dosage and Administration (2.5) in Full Prescribing Information*].

Renal Impairment

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

Hepatic Impairment

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

Patients with Parkinson's Disease or Lewy Body Dementia

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

DRUG ABUSE AND DEPENDENCE

Controlled Substance

INVEGA SUSTENNA® (paliperidone) is not a controlled substance.

Abuse

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

Dependence

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

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OVERDOSAGE

Human Experience

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

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

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

Management of Overdosage

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

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

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

Product of Ireland

Manufactured by:
Janssen Pharmaceutica NV
Beerse, Belgium

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FROM THE CHAIRMAN

Supporting Our Future

Children are the world's most valuable resource and its best hope for the future.

—John F. Kennedy

Once you become a parent, this quote becomes even more poignant. You recognize how your voice, actions, and presence affect your children—both negatively and positively—and you desire to protect them, invest in them, and nurture them. Indeed, research repeatedly shows how environment and social issues affect their growth, starting at the earliest ages.

It is, therefore, why this issue addresses so many facets of child and adolescent psychiatry. During the pandemic, children's mental health has taken center stage. The media continue to feature stories on the rising number of youth suicides, the impact of quarantining and subsequent reentry, substance use and misuse, and issues associated with social media.

In the Special Report, Martin P. Paulus, MD, and colleagues tackle the complicated issue of screen time, asking, "Is it friend or foe?" Screens were vital in our attempts to hold onto normalcy during the pandemic, allowing children and teenagers to attend school virtually and visit with family. It helped maintain connections. Yet, studies have demonstrated that too much screen time can be deleterious, and social media's role in depression and drug use among teenagers has been called into question. Paulus et al attempt to make sense of the data and provide useful tips for working with your patients. Chaired by Karen Dineen Wagner, MD, PhD, the Special Report also sheds light on new research in depression, digital therapeutics for autism, integrating well-being into child and adolescent psychiatry, and special issues in caring for immigrant children.

This issue also features pieces on issues that affect all patients, regardless of age. For instance, our popular Tales From the Clinic series is back, this time discussing how psychotherapeutic, pharmacological, and comorbidity factors interplay. Similarly, Dustin DeMoss, DO, and colleagues explore psychiatric implications of vitamin B₁₂ deficiency. And we look at the ABCs of vaping, as well as diagnostic challenges associated with bipolar disorder.

Hopefully the insights and clinical pearls you will find cover-to-cover in this issue of *Psychiatric Times*™ will help you provide the best future possible for all of your patients—young and old alike. □

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FROM THE EDITOR

Epigenetics Collide With Pharmacogenomics

John J. Miller, MD | Editor in Chief

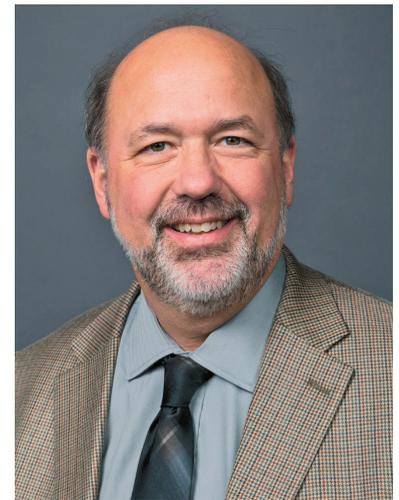
Let me begin with my conclusion: The current clinical use of pharmacogenomic testing in psychiatry to determine a metabolic enzyme's activity to choose a medication to prescribe is not evidence based.

Medicine and Science Continue to Evolve

The history of medicine, and of the edifice of science upon which much of medicine is built, is a never-ending work in progress that involves the continued evolution of hypotheses and rewriting of paradigms as they are disproven and become outdated. In 1869, Dmitri Mendeleev, PhD, a brilliant Russian chemist, submitted the first periodic table of the elements to the scientific community; this was a quantum leap forward in understanding the physical nature of reality. Over the next 25 years, scientists bragged about how the physical nature of reality was finally understood, and all that was left was filling in the gaps.

This paradigm was rocked in 1895 when German physicist Wilhelm Röntgen, PhD, discovered x-rays. This began the new chapter of the electromagnetic spectrum of radiation, which culminated in our understanding of discrete bands with unique properties and energies: radio waves, microwaves, infrared, visible light, ultraviolet, x-rays, and gamma rays. This new science enabled the development of the atomic bomb.

My favorite story about medicine's changing understanding revolves around the cause of gastric ulcers. When I was in medical school, the etiology was believed to be due to stress and/or spicy foods. In the early 1980s, J. Robin Warren, MBBS, and Barry J. Marshall, MB BS, AC, FRACP, FRS, FAA, of Australia discovered *Helicobacter pylori* residing in the stomachs of patients with ulcers and gastritis; they eventually confirmed that this bacterium was the



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etiologic agent for these disorders, and ultimately received the 2005 Nobel Prize in Physiology or Medicine.¹ They ultimately transformed the treatment of gastritis by proving antibiotics were an effective treatment in most cases.

Pharmacogenomics and the Human Genome

Since my college years I have always enjoyed a passion for molecular genetics. In the early 1990s, I reveled in the growing understanding of the cytochrome P450 (CYP450) metabolic enzyme system and the subsequent identification and classification of the 57 human isoforms. In psychiatry, 5 CYP450 enzymes surfaced as significant for many medications: CYP450 1A2, 2C9, 2C19, 2D6, and 3A4. Further research revealed that 2 of these enzymes had significant genetic polymorphisms: CYP2D6 with approximately 100 different alleles, and CYP2C19 with approximately 35 alleles.

With the complete sequencing of



It's been raining in my mind for months now. Me negative?... Nah...

Actor portrayal.

ADHD

It can be quite overwhelming to come face-to-face with the complexity of ADHD...

ADHD is a complex disorder in adults¹

Adult ADHD carries a profound functional and psychosocial burden—particularly in the presence of comorbidities.² ADHD has been found to be associated with an elevated all-cause mortality risk.³ This risk increases with later age of diagnosis, in adulthood, and when comorbid conditions are present.³



Up to **80%** of adult patients with ADHD may have a comorbid psychiatric condition.²



Over **50%** may have multiple psychiatric comorbidities⁴; the most common include^{2,5}:

- Substance use disorder
- Mood disorders (eg, bipolar disorder, depression, dysthymia)
- Anxiety disorders
- Phobias

These comorbidities present significant clinical challenges, since their co-occurrence is linked to more severe illness course than ADHD or psychiatric disorders alone.²

Sign up to find our more at TEAM-ADHD.com/unmask

If you ask the right questions, together we can find the answers

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the human genome in 2003, the field of pharmacogenomics exploded. Over the ensuing decade, DNA sequencing technology continued to improve, and the varying gene alleles of the CYP450 enzymes, especially *CYP450* 2C19 and 2D6, could be identified for a specific patient.² This led to the development of pharmacogenetic testing on a commercial scale, with the accompanying message by invested labs that the genetic phenotypic information for metabolic enzymes allowed the psychiatric clinician to make a more informed choice of which antidepressant or antipsychotic would be best for their patient based on the information from the patient's 2 sequenced genes for each metabolic enzyme.

The Clinical Pharmacogenetics Implementation Consortium was established in 2009 to vet pharmacogenomic data as clinically actionable versus simply interesting.³ Yet this organization and its database has been virtually ignored by commercial labs and clinical prescribers who choose to believe all the results in pharmacogenomic test reports are clinically accurate. For instance, a recent review concluded, "Genotype-assisted forecasts cannot therefore be used with confidence to replace actual phenotype measurements."⁴ For a more comprehensive discussion of this current controversy, please see my *Psychiatric Times*™ June 2019 editorial titled "Psychiatric Pharmacogenomic Testing: The Evidence Base."

A New Chapter: Enter Epigenetics

Unfortunately, the anticipated exciting discoveries aimed to better understand and treat human disease as a result of completed sequencing of the human genome never really materialized. Rather, geneticists learned that the sequenced 3 billion base pairs in the human genome was simply a static code. This code contains all of the genetic information to create a complete person, but it served more as data on a computer's hard drive that needed complex software to decipher, from conception until death.

Over the past 20 years, the exploding field of epigenetics has opened an entirely new chapter in science and has created many more questions than it has answered. We have learned it serves as the software. (Please see my *Psychiatric*

Times™ June 2021 editorial, "Exploring the Epigenetic Paradigm Shift," for a detailed review.)

When the new field of epigenetics collided with the well-established field of pharmacogenomics, the result was a novel explosion of information and understanding that is helping to shed light on how these fields are intimately interwoven into the human genomics story. In 2013 at the 2nd International Genomic Medicine Conference, it was concluded⁵:

Pharmacogenomics deal with various biological factors related to drug metabolism including drug transporters, the contribution of receptors and drug metabolizing enzymes with polymorphisms that affect the drug response in a variety of diseases; all of these parameters are under epigenetic control.

It turns out that epigenetic modifications due to environmental factors, life stress, disease states, and epigenetic heritability play a significant role on the ultimate expression of a particular gene and will determine that gene's phenotype—not the unchanging gene's DNA sequence that pharmacogenomic testing reports use to determine a patient's putative phenotype. These epigenetic modifications include DNA methylation of the gene's promoter sequence, the addition of various chemical structures (such as the covalent addition of an acetyl or methyl group) to histones, and noncoding microRNAs.

Epigenetics and Gene Production Plasticity

It is well established in humans that, throughout the course of an individual's life, numerous events, environmental conditions, and processes can reversibly add or remove methyl groups from a gene's promoter sequence. The more methyl groups that are added, the more gene expression is shut down, even to the point that the gene expression can be turned off. Later, the methyl groups can be removed from the promoter sequence and, as they are, the gene will start to be transcribed once again. Histone modifications can serve to increase access to a gene to increase its gene product expression, or to further hide the gene from the transcrip-

tion machinery. Finally, microRNAs can neutralize a posttranscriptional mRNA gene product effectively eliminating any further activity by that mRNA.⁶

One group used mice to test their hypothesis that epigenetic gene regulation of CYP450 enzymes involved in drug metabolism could explain the reduced liver function in aging that increases the risk of adverse drug reactions. The authors initially reviewed the literature on epigenome-wide studies of human blood, and they determined that CYP450 2E1 demonstrates the most epigenetic changes with age in humans. Mouse livers from mice aged 4 to 32 months were assayed for clearance of chlorzoxazone—a CYP2E1 specific probe—and compared the clearance with epigenetic changes in mouse *CYP2E1* gene with age. They concluded that age-related epigenetic changes in mice may influence hepatic drug metabolism function.⁷

Is This a Story of Mice and Men?

If pharmacogenomic testing accurately predicted the functional phenotype of CYP450 and other metabolic enzymes, it would be of great value for the practicing clinician. However, our current understanding of the unchanging DNA sequence of our personal 3 billion base pair genome does not translate into a fixed and unchanging phenotype based on the genotype.

A classic paper by Preskorn et al⁸ provided strong evidence that an individual's functional phenotype at any point in time can be quite different from what the DNA genetic sequence genotype would predict. In their study, patients on venlafaxine extended release (ER) were genotyped for *CYP2D6* by traditional pharmacogenomic testing. After up to 8 weeks on venlafaxine ER, patients were phenotyped for CYP2D6 by the established protocol of serum drug level ratios of O-desmethylvenlafaxine and venlafaxine. With this assay, CYP2D6 poor metabolizer phenotype was defined as O-desmethylvenlafaxine to venlafaxine ratio of less than 1.

Although only 4% (35/900) of patients were genotypic CYP2D6 poor metabolizers, 27% (243/900) were phenotypic CYP2D6 poor metabolizers based on the serum level assay. The authors concluded that pheno-

conversion to CYP2D6 poor metabolizer status occurred in 209 of 865 individuals (24%) with a simultaneous pharmacogenomic test documenting them as CYP2D6 non-poor metabolizer genotype.

Conclusions

Many possibilities exist to explain this discrepancy. The list of putative causes of this dramatic phenoconversion from non-poor metabolizer to poor metabolizer is beyond the scope of this editorial. However, it is entirely possible that epigenetic changes to the individual's 2 *CYP450* 2D6 genes may explain some of these phenoconversions. From our current understanding of epigenetic processes on the stable and unchanging DNA genome, the promoter sequence of an individual's 2 *CYP450* 2D6 genes could have been highly methylated, hence decreasing gene production of the enzyme CYP450 2D6. For another individual, histone modifications could be decreasing transcription access to these same genes. Additionally, one person may have triggered excessive production of microRNA that neutralized and effectively eliminated the mRNA transcription product that would have otherwise been further processed into a CYP450 2D6 enzyme.

As medicine and science continue to evolve and our hypotheses continue to get refined and updated, more surprises most certainly await us. The collision of epigenetics with pharmacogenomics has once again humbled us.

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Narcolepsy Management: The Roles Neurologists & Psychiatrists Play

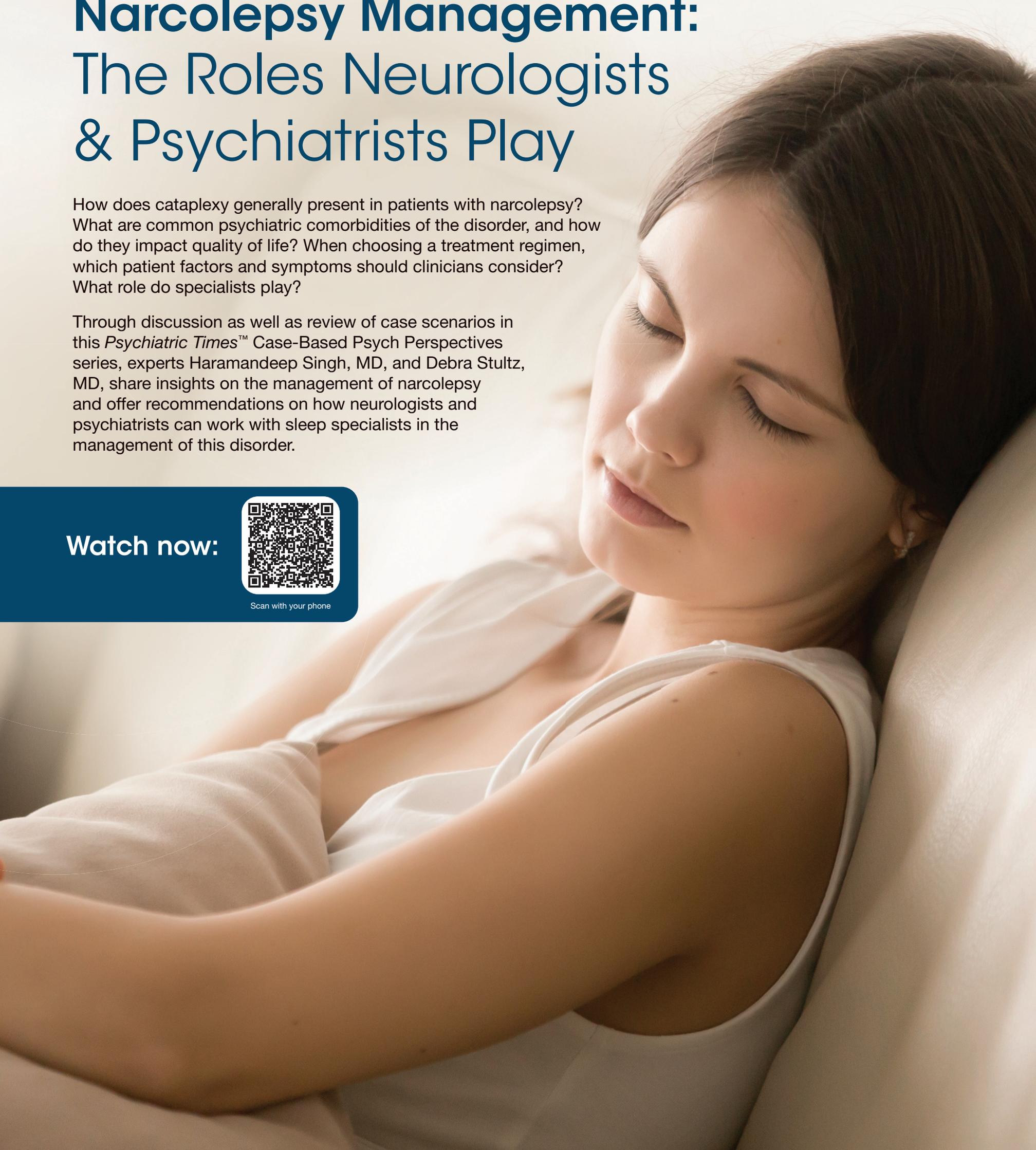
How does cataplexy generally present in patients with narcolepsy? What are common psychiatric comorbidities of the disorder, and how do they impact quality of life? When choosing a treatment regimen, which patient factors and symptoms should clinicians consider? What role do specialists play?

Through discussion as well as review of case scenarios in this *Psychiatric Times*™ Case-Based Psych Perspectives series, experts Haramandeeep Singh, MD, and Debra Stultz, MD, share insights on the management of narcolepsy and offer recommendations on how neurologists and psychiatrists can work with sleep specialists in the management of this disorder.

Watch now:



Scan with your phone



Is video game addiction a disorder?

Continued from Cover

This tragic story joins others from around the world. In South Korea, a couple was arrested for being so obsessed with video games that their infant daughter died of malnutrition.² As Korean internet gaming cafes grew in popularity, so did stories of players who wore diapers just so they could avoid taking bathroom breaks.² Using the results of a survey of more than 2000 South Korean middle school students, close to 6% were classified as having a gaming disorder, and another 8% were considered to be at high risk for the disorder.³

In response to statistics like these, the World Health Organization (WHO) in 2018 officially included internet gaming disorder (IGD) in *International Classification of Diseases, 11th Edition*, noting that the disorder resulted in “marked distress or significant impairment in personal, family, social, educational, or occupational functioning.” WHO further noted other associated health concerns, including insufficient physical activity, poor diet, problems with eyesight and hearing, musculoskeletal problems, sleep deprivation, aggressive behavior, and depression, as well as poor psychosocial functioning.⁴

Mental health providers in numerous countries, including South Korea and China, welcomed WHO’s decision, saying it formalized a way to better understand the problem and support patients. In the United States, however, the American

Psychiatric Association (APA) has been hesitant to label gaming addiction as a psychiatric disorder. So far, gambling is the only behavioral addiction identified as a disorder by the APA; it was added as a DSM-5 disorder in 2013.

Only 0.3% to 1% of the worldwide population qualifies for a diagnosis of acute IGD, according to a 2017 international survey.⁵ A 2020 American Psychological Association survey of 214 scholars revealed a lack of consensus on gaming addiction.⁶ About 49.7% agreed with the DSM-5 criteria, and 56.5% supported WHO’s disorder diagnosis. Similarly, 60.8% of scholars agreed that pathological video game use could be a mental health problem, but 30.4% were skeptical.⁶

Clearly, opinions differ, contributing to ongoing confusion and making it difficult for psychiatrists to accurately diagnose and address symptoms.

Growing Popularity or Problem?

The earliest video game dates back to 1940, when an electromechanical machine was introduced at the New York World’s Fair. Public arcades remained the most popular places for gaming until the 1970s and 1980s, when Atari’s new video computer system brought games into homes. Then, video games found a new niche online with the rise of the internet, and it has evolved even further with mobile phones, which makes it easy to play anywhere, anytime. Today, the array of video game genres is vast, including role playing, action-adventure, first-person shooters, and strategy.

As a result, sales of video game products in the United States have swelled over the years. In 2020, consumers spent \$57 billion on video games, beating 2019 sales by 27%,⁷ and the trend continues, with Americans spending \$14.92 billion in the first quarter of 2021—a 30% increase over the first quarter of 2020.⁸ Globally, early 2020 projections were exceeded by \$15.6 billion to \$174.9 billion in revenues, thanks, in part, to the COVID-19 pandemic. Sales show no signs of stopping: Projections of 2023 sales are more than \$217 billion.⁹

Brigham Young University recently released results of a 6-year study, the longest of its kind, on the effects of video game play and the trajectories of addiction. The results show that 10% of video game players exhibited pathological behavior. Pathological behavior includes playing video games excessively, which increases risk of depression, aggression, shyness, and anxiety, and is associated with the worst outcomes over time. The researchers concluded that it is not a “one-size-fits-all disorder.” Players who displayed pathological behavior tended to be males with low levels of prosocial behavior. They exhibited the worst long-term outcomes, with higher risks of depression, aggression, shyness, problematic cell phone usage, and anxiety when compared with the nonpathological control group.¹⁰

In terms of assessment, DSM-5 has a 9-item

IGD Scale used to assess symptoms of gaming addiction. Gaming must cause “significant impairment or distress” in several areas of a person’s life, with the expression of at least 5 symptoms within 1 year for a diagnosis (**Table 1**). Numerous risk factors are associated with IGD (**Table 2**).¹¹

“They exhibited the worst long-term outcomes, with higher risks of depression, aggression, shyness, problematic cell phone usage, and anxiety.”

Other risk factors include underlying psychiatric illness, such as anxiety or depression, and certain personality traits such as neuroticism, anxiety, sensation-seeking behavior, aggression, and impulsivity.¹² Those who play massively multiplayer online role-playing games are also at increased risk, compared with gamers who do not.¹³ People with severe attention-deficit/hyperactivity disorder (ADHD) symptoms, compared with those with less severe ADHD symptoms, are more at risk of developing video game addiction and suffering its negative consequences.¹⁴

How Video Games Affect the Brain

A 2017 systematic review of 116 articles linked video game use to several structural and functional brain changes, involving attention, cognitive control, visuospatial skills, cognitive workload, and reward processes.¹⁵

Compared with nonplayers, gamers were found to have improved attention and visuospatial skills, likely due to increased blood flow and volumetric changes observed in the dorsolateral prefrontal cortex. Researchers also found that video game play is closely tied to the brain’s reward system and involves mechanisms related to impulsivity and loss of control. Gamers had increased activation of several areas in the cortical ventral basal ganglia circuit, a prime network that influences reward-seeking behavior. The hippocampus, parahippocampus, and amygdala, which link emotions and memory to game-related cues, were also involved.¹⁵

The review noted negative outcomes associated with video game play, such as reduced recruitment in the anterior cingulate cortex, which can negatively affect attention. Exposure to violence in video games was shown to lower activity in the dorsolateral prefrontal cortex, causing behavioral inhibition, negative effects on social information processing, delays in development of certain brain areas, and lower verbal IQ.¹⁵

Other studies have noted the impact of video

Table 1. DSM-5’s Internet Gaming Disorder Scale

A diagnosis of internet gaming addiction requires the experience of 5 or more of these symptoms within 1 year:

- Preoccupation with gaming
- Withdrawal symptoms (eg, sadness, anxiety, irritability) when gaming is taken away or not available
- Tolerance, more gaming is needed to satisfy the urge
- Unsuccessful attempts to quit or reduce gaming
- Loss of interest in previously enjoyed activities due to gaming
- Continuing to game despite problems
- Deceiving family and friends about the amount of time spent gaming
- The use of gaming to relieve negative moods (eg, guilt, hopelessness)
- Risk, having jeopardized or lost a job or relationship due to gaming

games on the release of dopamine, the neurotransmitter associated with pleasure, learning, attention, reinforcement, and sensorimotor integration. For example, results of a 1998 study using radioligand and positron emission tomography (PET) scans found that dopamine levels were increased in the ventral striatum, which influences motivation and reward.¹⁶ Similarly, results of a 2011 study of 154 adolescents, all aged 14 years, leveraged functional MRI scans and found that frequent gamers had increased grey matter in the left ventral striatum of their brains, an effect similar to that present in the brains of gambling addicts.¹⁷ The study authors suggested that changes in dopamine receptors and brain reward pathways over time could cause players, particularly addicts, to build up a tolerance and experience less pleasure. This effect is similar to substance abuse addiction, as both exhibit reduced dopamine responses to stimuli.¹⁸

In addition to its effects on the brain, excessive gaming is associated with a variety of negative psychosocial effects. Studies have found that video game addicts tend to have poorer mental health and cognitive functioning, including poorer impulse control and more ADHD symptoms when compared with control groups. They also display increased emotional difficulties, such as depression and anxiety, feel more socially isolated, and are more likely to report symptoms indicative of problematic use with internet pornography.¹⁹

Results of a 2019 study in Germany showed a medium-sized positive correlation of potential problematic gaming with the presence of impaired psychological functioning; symptoms included depression, anxiety, and hostility. There was also a connection to maladaptive coping mechanisms (eg, self-blame, behavioral disengagement, denial, acceptance, substance use, self-distraction, and venting), overall negative affect, poor self-esteem, preference for solitude, and poor school performance. However, the authors cautioned about establishing causation, given that it was a cross-sectional study, and also warned that psychological dysfunction can be a cause or an effect of pathological gaming.²⁰

Aggressive Behavior

How video games influence aggressive behavior has been hotly debated for decades. Concerns that violent video games such as *Mortal Kombat* and *Night Trap* could increase aggression in children played

out in US Congressional hearings from 1993 to 1994. These led to the creation of the Entertainment Software Association, a trade group that created a standardized rating system of violence in video games.

Research conclusions are also divided on the topic of aggression. An article in the *Journal of Personality and Social Psychology* reviewed 2 studies and concluded that video games provided a dangerous medium for adopting aggressive solutions to conflicts. Video games, the authors wrote, caused short-term cognitive changes in the brain by priming aggressive thoughts. Long-term effects were created by reapplying aggression-related scripts learned during play time to real-life scenarios. Because players got to practice aggressive moves in real-time play, the authors concluded that playing violent video games was more dangerous than watching television or film violence.²¹

Authors of a 2019 study, however, countered this argument and found that no tipping point was associated with the engagement of a violent video game and an increase in aggressive behavior.²²

Although opinions and research conclusions remain divided, a clear constant remains: Males are generally more likely than females to develop video game addictions.¹¹ Gender differences may also play a role, particularly as it relates to anxiety during late adolescence. Although it is hard to generalize results due to the limited sample, results of a study suggested that boys who played video games experienced the least anxiety, while girls had the most, conditions that were exacerbated when playing with others.²³ Possible reasons could be that boys are more likely than girls to make friends online, feel more connected to friends during play, and use video games to engage with friends.²³

Results of another study indicated that internet gaming addiction seemed to shorten the length of leukocyte telomeres in adolescent Korean males, a result that could be attributed to changes in autonomic functions, such as catecholamine levels.²⁴ Telomeres are genetic components that act as

markers of cellular aging and are influenced by many factors, such as lifestyle changes and stress levels. Shorter telomere length is associated with increased pace of aging and increased incidence of diseases over time.

The Scope of the Problem

In 2017, a group of scholars wrote an open debate paper cautioning WHO against listing video game addiction as a disorder, as it could leave the

proverbial door wide open to pathologizing other conditions, such as addictions to sex and food.²⁵ Video game addiction rates are generally low, they argued, and there was a lack of consensus on the addiction's symptoms and assessment. Criteria used to support the diagnosis relied too heavily on benchmarks for substance abuse and gambling disorders, they wrote. The scholars claimed that this distinction would shift the focus of video game addiction research to that of a confirmatory approach, rather than an exploratory one. They also cautioned that the label of disorder would create a moral panic and could trigger premature diagnoses, in addition to creating a stigma for children and youth who play video games as "part of a normal, healthy life."

Although individuals in China and South Korea see IGD as a dangerous and growing problem, it does not seem to attract the same concern in the United States and elsewhere around the world. Much of this difference in perspective could come down to simple cultural differences. In China, professional esports players train upward of 14 hours a day for a chance to compete in arenas like the League of Legends world championships, where they can earn hundreds of thousands of dollars.²⁶ In South Korea, watching esports competitions is more popular than watching other kinds of television programs. For many individuals raised in working-class families in South Korea, a nation in which access to higher education is intensely competitive, the idea of going professional serves as a way to escape their circumstances.²⁷

Table 2.
Risk Factors Associated With IGD

- Functional and dysfunctional impulsivity
- Belief self-control
- Anxiety
- Money spent on gaming
- Weekday game time
- Offline community meeting attendance
- Game community membership

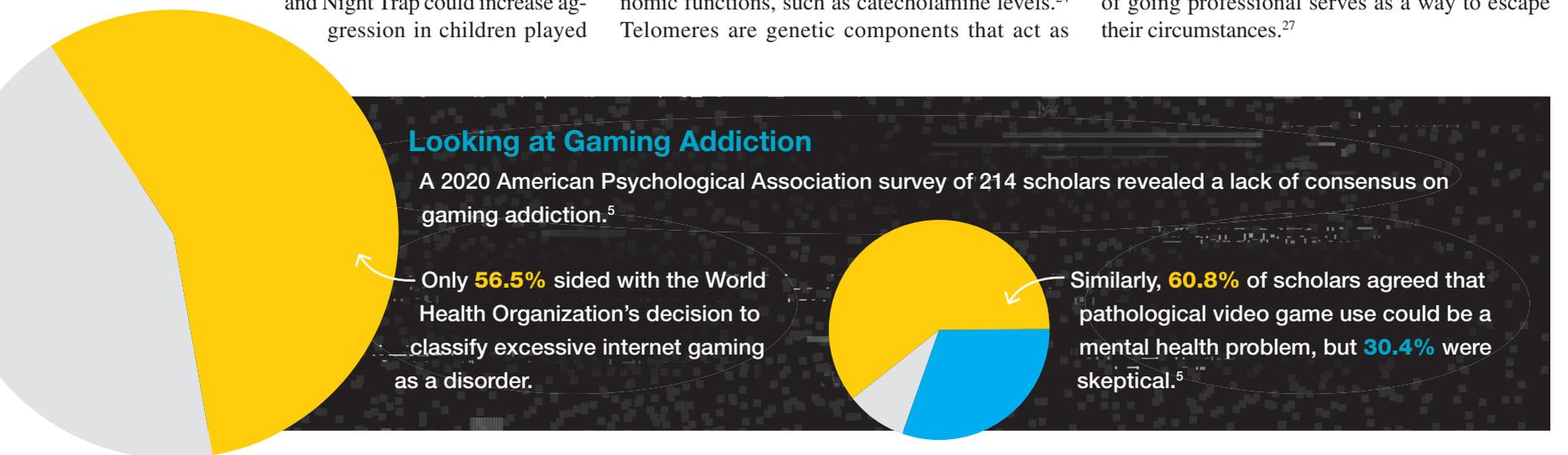


Table 3. Signs That Video Game Use Has Become Disruptive

- Mood changes, eg, depression, irritability, increased anger outbursts, poor tolerance, aggression
- Poor hygiene, lack of self-care, reduced exercise
- Lack of structure during the day
- Isolative or reduced social behavior
- Impaired attention in other areas, procrastination, and/or neglect of other tasks
- Fatigue
- Reduced appetite, weight changes
- Problems at work or academic decline
- Increased conflicts at home with family over video game use

Perhaps the stakes are not as high in the United States, where passion for the games may be among the strongest motivations to play. According to article authors writing on behalf of the American Psychological Association, 97% of children and adolescents aged 2 to 17 in the United States play video games for at least 1 hour a day. They noted that playing video games could improve cognitive skills, problem-solving abilities, mood, resilience, motivation, social skills, and overall well-being.²⁸

A recent study by researchers at the University of Oxford, collaborating with 2 video game companies, surveyed more than 3270 players in the United States, United Kingdom, and Canada to measure their well-being, self-reported play, and motivational experiences during play.²⁹ They found that players genuinely enjoyed playing the games, which had a significant positive impact on a player's well-being. Further, the findings were aligned with past research results suggesting that people whose psychological needs are not being met in the real world might report negative well-being from play.

Studies have also shown that the length of play time and the type of video game have an impact on the game's negative or positive effect. Games that featured more online social interaction resulted in fewer problematic gaming symptoms. Males playing nonsocial games appeared to have more social anxiety. Females who played social games had less social anxiety and loneliness but exhibited lower self-esteem than their male counterparts.³⁰

Of note, interest is growing in using video games to treat a range of mental health conditions in youth and adults, such as ADHD, depression, and posttraumatic stress disorder.

Treating Video Game Addiction

In some cases, classifying video game addiction as

a disorder could be useful, even if only a small percentage of people experience it. Such a distinction would allow clinicians to detect and treat other coexisting conditions, such as depression, anxiety, and substance addiction.

When considering a potential problem with video games, clinicians should look for symptoms and signs that video game use has become disruptive (Table 3).

Several treatment options are available to address video game addiction, including cognitive behavioral therapy, family therapy, motivational interviewing, and solution-focused therapy, as well as combinations of these. Additionally, Online Gamers Anonymous, a 12-step recovery program established in 2002, offers an approach to break addiction similar to that of Alcoholics Anonymous and Narcotics Anonymous.

For example, a study examined the efficacy of a 9-day self-discovery camp for adolescents that included 14 cognitive behavioral therapy sessions, 8 personal counseling sessions, 3 medical lectures, a gaming workshop, engagement in positive gaming activities, and abstinence from games during the stay.³¹ Researchers found that participation in this camp led to decreased gaming time at a 3-month follow-up and that age of onset of IGD and problem recognition were correlated.

Bupropion, a medication commonly used to treat depression and ADHD, has shown some positive effect in treating symptoms of video game addiction. Study results have shown some benefit from treating comorbid video game addiction and ADHD with methylphenidate.³² Unfortunately, these results highlight the paucity of well-designed treatment outcome studies, with limited evidence for the drugs' effectiveness. Additional studies, ones with better design, are needed before these medications are FDA approved.

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Psychiatry in the Year 2500

Continued from Cover

guess what might be possible in 2500, but also to imagine how 26th-century psychiatrists might perceive how we think and practice during our psychiatric moments in time.

Overall, we hope that they might view us sympathetically, as trying hard to do good work with what we have, constrained by our limited concepts; by our physics, chemistry, biology, psychological, and social science tools; and by our socio-cultural-economic structures. This perspective reminds us that current theories, diagnoses, and methods of assessment, treatment, and prevention are at best temporary placeholders in the arc of psychiatric history, many destined to be replaced within a generation or 2.

Unable to search 2500's PubMed, we cannot cite the next half-millennium's scholarly publications. Although we are unable to foresee what are certain to be surprising discoveries, we can future-cast by extending contemporary research and technologies. We can also invoke developments envisioned by today's keenest scientists.¹ From such perspectives, what contemporary psychiatric sacred cows, practices, and professional delusions (or to be kinder, illusions) might 26th-century psychiatrists see as deserving to be thrown into the trash bin of psychiatric history?

Psychiatric Theories

In 2500, most of today's aminergic, cognitive, psychoanalytic, and family process theories are likely to be viewed as quaint^{2,3}; 26th-century psychiatry might view our biopsychosocial approach as a good start for an overarching framework, but as generally simplistic in details and understanding.⁴

By 2500, scientists may have clarified the mechanisms and impacts of genetic, epigenetic, and huge varieties of elusive physical and psychosocial environmental forces. We may know how psychobiological processes, from molecular to transpersonal over lifespans, influence psychiatric health. Consequently, models of the mind and brain, coping and adaptation, and family and social function will evolve accordingly. As more nuanced mechanisms are delineated, old theories will drop and new ones will emerge.

Conducting Psychiatric Assessments

In 2500, most of today's assessment methods will be considered archaic and excessively labor intensive. Predominantly dependent on prolonged self-reported histories elicited face to face, human-to-human psychiatric assessment interviews will be regarded as inefficient, incomplete, and remarkably error-prone, faulted for being susceptible to ubiquitous and influential biases and prejudices that color human thought.⁵

By 2500, such biases will have been (hopefully)

largely eliminated with the use of artificial intelligence (AI)-assisted assessment tools. Human assessors will come into play only after initial screening assessments have been completed. Constantly refined over years, mechanisms for obtaining dynamical biopsychosocial fingerprints might produce highly nuanced and individualized psychiatric profiles.⁶ Starting with genomic and epigenomic analyses in utero ("You on a Chip"),⁷ such fingerprints will utilize massive data stores, integrating information about neurobiology, temperament, coping styles, personality, and life events derived from individual, family, school, social connection, AI usage, and other registry sources. To all this might be added information from responses to individualized, virtual reality-based scenario simulations and from high-definition, whole-brain, dynamic scans assessing connectivity among numerous interacting brain regions. Each fingerprint will be compared with those of billions of individuals going back for generations.

"Overall, we hope that they might view us sympathetically, as trying hard to do good work with what we have, constrained by our limited concepts."

Making Diagnostic Formulations

In 2500, most of today's psychiatric diagnoses as compiled in *DSM-5* will be viewed as primitive, superficial descriptions at best, on par with antiquated terms like *rubor*, *calor*, and *dolor*, or perhaps *pneumonia* in general medicine.

By 2500, psychiatric diagnoses might be calculated along lines of precision psychiatry, encompassing individuals' cell-specific diagnoses, brain functional neuroanatomy and connectivity patterns, interpersonal interactions, life events, and appraisals of deviant behaviors, all contextualized within patients' micro- and macro-cultural frameworks. What we now call multiple comorbidities and varieties of major psychiatric disorders will be cast as highly elaborated and differentiated prototypical patterns.⁸ These patterns might calculate patients' stress-vulnerability balances and psychological reserves, indicate warning signs and risks, and predict the likelihood of a specific patient erupting in an episode of suicide or violence.

Looking at Treatments

By 2500, virtually all of today's psychiatric medication, somatic, and psychotherapeutic treatments will be viewed as archaic. Psychiatrists in 2500 will shudder at the hit-or-miss application and modest effectiveness of our biological and psychotherapeutic interventions as well as their many ad-

verse effects.³ They will find it hard to understand why clinicians in the early 21st century permitted patients with substantial psychic pain related to psychosis, depression, and cravings to suffer for days and weeks before being administered substantial relief.⁹ They will feel sorry that patients had to waste so much time in ineffective treatments (in addition to traveling to and from these treatments) and endure years of poor quality of life.

By the year 2500, psychiatric patients might access a host of wearable and implantable devices that both monitor ongoing status and administer experiential (eg, educational, interactive, psychotherapeutic) and direct biological interventions.^{10,11}

For reasons of efficiency and effectiveness, AI-based personalized robots (robotherapeutic i-BOTS¹²) and individualized game-based (i-SIM¹³) treatments might prevail. I-BOTS could provide social support and companionship on one hand, and, on the other, train patients to develop more effective social skills with specific individuals, individuals in general, and groups. Based on moment-to-moment data from personalized smartphones and auditory-visual-physiological sensors, these devices might detect when individuals experience difficulties and initiate first-order personal coaching, which might up-regulate to personalized psychotherapies. When i-BOTS sense that their resources are insufficient to adequately manage difficulties, they might signal a need for higher-level services to the patient's personal health concierge, formerly known as a primary care clinician, for triage to higher levels of care, including human clinicians, who can (as it were)

think outside the BOT.

By means of i-SIM therapeutics and virtual reality-based games, which could use holographic avatars to reenact earlier life events and current stressful interpersonal or other toxic environments, patients might learn to overcome fears, fixations, deficient emotional regulatory capacities, and other challenges.

For interventions requiring biologicals, the psychiatrists of 2500 may be able to tailor everything from medication types and dosing schedules to delivery systems and routes of administration, basing them on patient-centered analyses using genes, epigenetic patterns, brain circuitry, microbiomes, and psychosocial factors.¹⁴

Neurostimulatory interventions might feature stereotactic membrane-like skullcaps, capable of focusing deep ultrasound and other noninvasive stimuli at precise targets to promote local neogenesis.^{15,16} Optogenetic-guided retroviral interventions might enhance and sculpt specific brain nuclei and connection pathways.¹⁷ Umpteenth-generation CRISPR-like genetic interventions might reverse neuropathological processes associated with excessive pruning, dysregulated emotional and attentional centers, impulsivity, habit formation, and craving.¹⁸ Anti-neuroinflammatory agents and neuroplaque removers might inhibit and reverse degenerative and other psychiatric diseases,¹⁹ while indi-

“I hope these musings offer a perspective on our place in the history of psychiatry’s arc over time. We try to do the best we can with what we have, but we should not be self-satisfied about our efforts.”

visualized biomic brews might enhance healthier microbiomes.²⁰

Since unrelenting psychic pain in anxiety, mood, psychotic, and other disorders can activate and kindle terrifying, auto-traumatizing memory patterns (further augmenting posttraumatic stress disorder), patients in extreme psychic pain might be treated with psych-anesthetics. These agents might acutely alleviate psych-aches and induce therapeutic sleep, during which neurogenerative treatments might be applied.

With respect to treatment settings, few ambulatory patients will travel to clinicians’ offices or treatment centers, as virtually all interventions will be amenable to remote administration via teletreatment.^{21,22} Who would want to spend hours traveling to and from clinicians’ offices when 3-D telemedicine permits individual, tele-family, and tele-group therapy, even with participants in different locations, time zones, and continents?

When necessary, individuals who are highly disturbed will still be treated in specialized sanctuary-like medical treatment centers, usually for brief periods of time. Thanks to thorough assessments and deep data mining, extremely accurate assessments of needs and risks should be available for comprehensive discharge planning.

For socialization, education, training, and rehabilitation purposes, actual live human gatherings are likely to endure, as they have for many centuries.

The Promise of Prevention

In 2500, psychiatrists will view the early 21st century as virtually devoid of meaningful efforts to prevent psychiatric disorders. They will see that even when risk factors were well known and identified, few public health efforts were designed to minimize subsequent emergence of psychiatrist disorders.²³

By 2500 (with hopefully few biases), public health programs might identify and conduct more intensive assessments of high-risk neighborhoods, individuals, and families, and better provide indicated social and individual-based interventions. Thanks to immediate diagnoses of new pregnancies—and based on intrauterine genome and epigenetic scans as well as prenatal neurotemperamental assessments—precision interventions could assist with repairs based on advanced gene and epigenetic-manipulation techniques, while other individually tailored preventive interventions may also be implemented.

The Business of Psychiatry

In 2500, psychiatrists will find many of our contemporary practices for training, certifying, and recertifying psychiatrists to be laughable. They may appreciate that the quasi-apprentice model was probably the best that could be achieved under current circumstances. They will also note that, although well intended, cumbersome administra-

tive superstructures required that practitioners, academic faculty, trainees, and staff waste huge amounts of time in mind-numbing educational training and assessment rituals of unproven worth. They will further note that many tedious rituals revolved around scheduling, electronic medical records, charting, billing, ineffective meetings, and other time- and energy-swallowing administrative activities.

By 2500, based on increasingly effective and evidence-based learning methods, psychiatric training will utilize large numbers of simulators that will challenge, train, and meticulously assess trainees’ competencies in handling nuanced scenarios. Carefully constructed games will assess clinical decision-making and practice skills, knowledge, professionalism, communication, and systems-based care, each tailored for specific environments in which the clinicians serve. Certifications for specific necessary skills will be fluidly conducted, with in-house, on-the-job, and just-in-time learning, training and certification, renewable as new techniques and situations arise. Medical record keeping and other administrative functions will largely be allocated to natural language, administratively coded robo-scribes. These AI devices might also summarize and bring clinicians’ attention to salient portions of patients’ medical information before their scheduled encounters.²⁴

What Will Endure

In 2500, psychiatrists will find themselves sharing several characteristics with early 21st century psychiatrists. Given human nature, at least some citizens will still be prone to intermittently go off the rails; psychiatric disorders are still likely to be stigmatized; and psychiatric gurus are still likely to believe that there are too many patients, too few clinicians, too little knowledge, too few resources, and too little money for what they do. And, given human nature, in 2500 a high value will still be placed on deep, confiding, empathic interpersonal relationships, including clinician-patient relationships.²⁵

Conclusions and Implications

Why bother teaching the history of psychiatry by highlighting how future generations might appraise today’s psychiatric practices, and envisioning how they might practice? My intention is not to throw cold water on the sincere efforts of today’s dedicated, well-intentioned professionals. Rather, I hope these musings offer a perspective on our place in the history of psychiatry’s arc over time. We try to do the best we can with what we have, but we should not be self-satisfied about our efforts.

If any of these fanciful visions of future psychiatric practice seem worthwhile, they might provide aspirational goals, and motivation to realize these goals. And, if any of these fanciful visions seem dystopian, they might provoke us to develop better alternatives.

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Brief Summary of Prescribing Information for Drizalma Sprinkle™ (duloxetine delayed-release capsules). This Brief Summary does not include all the information needed to use Drizalma Sprinkle™ safely and effectively. See full Prescribing Information for Drizalma Sprinkle™.

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

See full prescribing information for complete boxed warning.

Increased risk of suicidal thinking and behavior in pediatric and young adult patients taking antidepressants.

Closely monitor all antidepressant-treated patients for clinical worsening and for emergence of suicidal thoughts and behaviors.

INDICATIONS AND USAGE

Drizalma Sprinkle™ (duloxetine delayed-release capsules) is a serotonin and norepinephrine reuptake inhibitor (SNRI) indicated for:

- Major Depressive Disorder (MDD) in adults
- Generalized Anxiety Disorder (GAD) in adults and pediatric patients aged 7 to 17 years old
- Diabetic Peripheral Neuropathic Pain (DPNP) in adults
- Chronic Musculoskeletal Pain in adults

CONTRAINDICATIONS

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

DOSAGE AND ADMINISTRATION

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

WARNINGS AND PRECAUTIONS

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

- **Severe Skin Reactions:** Severe skin reactions, including erythema multiforme and Stevens-Johnson Syndrome, can occur with duloxetine. Drizalma Sprinkle™ should be discontinued at the first appearance of blisters, peeling rash, mucosal erosions, or any other sign of hypersensitivity if no other etiology can be identified
- **Discontinuation Syndrome:** Taper dose when possible and monitor for discontinuation symptoms
- **Activation of Mania or Hypomania:** Use cautiously in patients with bipolar disorder. Caution patients about the risk of activation of mania/hypomania
- **Angle-Closure Glaucoma:** Avoid use of antidepressants, including Drizalma Sprinkle™, in patients with untreated anatomically narrow angles
- **Seizures:** Prescribe with care in patients with a history of seizure disorder
- **Blood Pressure:** Monitor blood pressure prior to initiating treatment and periodically throughout treatment
- **Hyponatremia:** Can occur in association with SIADH. Cases of hyponatremia have been reported
- **Glucose Control in Diabetes:** In diabetic peripheral neuropathic pain patients, small increases in fasting blood glucose and HbA_{1c} have been observed

ADVERSE REACTIONS

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

DRUG INTERACTIONS

- Potent CYP1A2 Inhibitors: Avoid concomitant use
- CYP2D6 Substrates: Consider dose reduction with concomitant use

USE IN SPECIFIC POPULATIONS

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

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

Please read full Prescribing Information and Medication Guide for Drizalma Sprinkle™ and discuss any questions with your doctor.

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CHILD AND ADOLESCENT PSYCHIATRY

Supporting Youth: New Findings in Youth Depression and Beyond

» Karen Dineen Wagner, MD, PhD

Child and adolescent psychiatry has always been important, and maybe it is even more so since the pandemic. As noted in an earlier Child & Adolescent Psychiatry column, COVID-19 has brought a complex array of factors (ie, uncertainty, social isolation, and parental angst) that have impacted youth mental health. We know predictability is a stabilizing force for children and adolescents, and that has been disrupted since the start of the pandemic. We likely will see an increased need for mental health care in the postpandemic period. This article summarizing new research and this Special Report will help support efforts in providing optimal care to our patients.

Depression Research: What's New

Several recent studies provide clinically relevant information about depression in children and adolescents on a range of topics including family history, long-term outcomes, ketamine treatment, and COVID-19's impact on depression and suicide risk.

Multigenerational Family History

It is well known that a family history of depression increases risk of depression for offspring. A recent retrospective study examined the association of multigenerational family history of depression and lifetime depressive disorders in children.¹ Data was obtained from the Adolescent Brain Cognitive Development (ABCD), which included psychiatric assessments of 11,200 children (mean age 9.9 years). Participants' parents provided information about depression history in second-degree and first-degree relatives (ie, grandparent's generation and parent's generation).

Risk of depressive disorders increased with a multigenerational family history of depression. The weighted prevalence of depressive disorder and suicidal behavior were 3.8% and 5.0%, respectively, when neither parent/grandparent generation had depression; 5.5% and

7.2% when grandparent generation had depression; 10.4% and 12.1% when parent generation had depression, and 13.3% and 15.0% when both parent/grandparent generations had depression. These findings reaffirm the importance of obtaining a family history when assessing children.

Long-Term Outcomes

Another recent study added to the expanding literature about the adverse consequences of depression in youth. In this study, the long-term outcomes of childhood/adolescent depression were examined using data from the Great Smokey Mountains Study, a longitudinal representative study of children in 11 rural counties of North Carolina.² The analysis included 1420 participants from 3 cohorts of children aged 9, 11, and 13 years. Annual assessments were conducted until age 16; assessments were then conducted at ages 19, 21, 25, and 30 years.

The Child and Adolescent Psychiatric Assessment was used to obtain information regarding childhood depression status, other psychiatric disorders, service use, and adversities/hardships, which included low socioeconomic status, unstable family structure, family dysfunction, family maltreatment, and peer victimization. Adult psychiatric disorders were assessed using the Young Adult Psychiatric Assessment. Adult functioning including health, risky/illegal behaviors, wealth (financial/educational), and social function were also assessed.

By age 16, 7.7% of the participants met full criteria for a depressive disorder (ie, major depression, dysthymia, or depression NOS). Childhood/adolescent depression was associated with other psychiatric disorders such as anxiety disorders, attention-deficit/hyperactivity disorder, oppositional defiant conduct disorder, substance use disorder, as well as adversities/hardships. Researchers found child/adolescent depression was associated with higher rates of adult anxiety, depression and substance use disorders, as well as worse functional outcomes (ie, general health, risky/criminal behavior, financial/educational status, and poor social functioning). No sex-spe-



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cific associations between childhood/adolescent depression and adult outcomes were found. Adolescent-onset depression was associated with more adverse adult outcomes than childhood-onset depression. Importantly, youth with childhood/adolescent depression who received specialty mental health services had a lower risk for any adult psychiatric disorder, but there was negligible effect on functional outcomes.

Ketamine in Adolescents

There are very limited data available in the adolescent population on ketamine. Dwyer et al³ conducted the first controlled trial of intravenous ketamine for adolescent treatment-resistant depression. Participants (n=17) were aged 13 to 17 years and had treatment-resistant depression, which was defined as failure to respond to at least 1 prior 8-week trial of antidepressants at therapeutic doses. The average number of failed prior antidepressants was 3.2. Depression was fairly chronic in these adolescents, with an average duration of 21 months for the current episode.

In the randomized, double-blind, single-dose crossover trial, adolescents received a single intravenous infusion of either ketamine (0.5 milligrams per kilogram over 40 minutes) or midazolam (0.045 milligrams per kilogram over 40 minutes) and the alternate compound 2 weeks later. Adolescents remained on their current medication during the trial; the majority were on antidepressant medication. The primary outcome measure was the score on the Montgomery-Asberg Depression Rating Scale (MADRS) 24 hours following treatment.

Depressive symptoms were significantly reduced 24 hours after a single ketamine infusion compared with midazolam. Clinical response (defined as more than a 50% reduction in MADRS score within 3 days following treatment) was significantly higher for ketamine than midazolam: 76% and 35%, respectively. MADRS ratings after ketamine were significantly lower at each post-baseline time point up to day 14 as compared with midazolam. Significant dissociative symptoms were found with ketamine, and were time limited, with an elevation at the 1-hour time point and return to baseline by the 2-hour time point. Based on these findings, large scale controlled trials of ketamine for adolescent treatment resistant depression are warranted.

Depression and Suicide

To address the concern of COVID-19's impact on youth, a recent study examined changes in depression and suicide risk screening, as well as percentage of posi-

tive screens during the COVID-19 pandemic.⁴ Electronic health record data were obtained from a large pediatric primary care network from Children's Hospital of Philadelphia, which included 29 urban, suburban, and semirural practices. Screening for depression and suicide risk during primary care visits for adolescents aged 12 to 21 years was compared for the periods of June to December 2019 (prepandemic n=45,504) and June to December 2020 (pandemic n=47,684). The Patient Health Questionnaire – Modified for Teens (PHQ-9-M) was used to screen for depression symptoms and suicide risk.

Depression screening rates during well visits declined from 77.6% to 75.8% during the pandemic period but gradually increased to prepandemic levels. There was an increase in the percentage of adolescents screening positive for moderate-to-severe depression—from 5.0% in prepandemic period to 6.2% in the pandemic period—particularly for female, non-Hispanic Black, and non-Hispanic White adolescents. Similarly, there was an increase in positive suicide risk screens from 6.1% to 7.1%, which was greater among female than male adolescents.

These findings demonstrates the importance of routine screening for depression and suicide in adolescents, especially during this pandemic period.

Concluding Thoughts

New research is critical to informing and optimizing care. The information in this Special Report will further enable you to address the mental health needs of children and adolescents.

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Screen Media Activity in Youth: Friend or Fiend?

» Martin P. Paulus, MD; Marc N. Potenza, MD, PhD; and Kara S. Bagot, MD

Spending time watching television, engrossed in a game on a tablet, glued to a gaming console, or messaging friends with a smartphone have become quintessential recreational activities of children and adolescents.¹ Screen media activity (SMA) consumes about 40% to 60% of after-school time,² and nearly 97% of US youth have at least 1 electronic item in their bedroom.³ However, SMA is highly diverse and continues to change over time.⁴ For example, over the past 4 years, the percentage of young individuals who say they watch online videos “every day” has more than doubled from 24% to 56% among 8- to 12-year-olds, and increased from 34% to 69% among 13- to 18-year-olds. Moreover, 70% of boys (aged 8 to 18 years) say they enjoy playing video games “a lot,” compared with 23% of girls aged 8 to 18; while 73% of girls say they enjoy listening to music “a lot,” compared with 59% of boys.

Conflicting Conclusions

Considerable debate has emerged regarding the relationships between SMA and psychological and social problems.^{5,6} Internalizing and externalizing⁷ symptoms are important aspects of youth mental health that signal the potential emergence or presence of significant psychiatric concerns. Internalizing problems are characterized by withdrawal and may include depression, anxiety, and somatization. Externalizing problems refer to behavioral issues such as impulsiveness, rule-breaking, and aggressiveness.

Reviewing the literature, Zink and colleagues⁸ reported that some types of SMA were associated with internalizing symptoms but not others, such as watching television. Others reported that high social media use was associated with more depressive features, panic symptomatology, delinquent behaviors, and family conflict, and lower levels of family and friend support,⁹ which is consistent with the observation that using social media for more than 3 hours per day was associated with internalizing problems.¹⁰ Greater SMA has been associated with decreased sleep duration, increased sleep onset latency, excessive sleepiness, insomnia, and overall sleep disturbance symptom severity.¹¹ In a recent systematic review of reviews, those individuals who engaged in more SMA, and especially television-related SMA, reported higher energy intake, poor diet, obesity and adiposity, and poorer quality of life (Table).¹² In the same review, general SMA was moderately related to depression, except for social media use, which demonstrated a weak association.

At the same time, there was weak evidence for relationships between SMA and behavioral problems, anxiety, hyperactivity, inattention, low self-esteem, poor well-being, and psychosocial health. Authors found that there was insufficient evidence for associations between SMA and eating disorders, suicidal ideation, cardiovascular risk factors, asthma, or pain. The investigators concluded that there is limited (ie, weak) evidence that small amounts of daily screen time are not harmful and may have some benefits.

A recent meta-analysis found that while overall SMA was not associated with academic performance, youth reporting more television viewing and gaming had poorer composite academic performance, whereas adolescents viewing more television had lower language and mathematics scores.¹³ Taken together, these recent studies seem to arrive at conflicting conclusions regarding the effects of SMA on mental or physical health and academic performance. So what is SMA, friend or fiend?

Evaluating Research

In considering these studies, it is important to step back and ask what we know and how we know it. To date, most research focused on SMA utilizes surveys or cross-sectional study designs, which provide some interesting information but cannot resolve causality or the directionality of relationships. In other words, we do not know whether mental and physical health issues precede and drive SMA-related behaviors, or if SMA behaviors result in mental and physical symptoms. Moreover, SMA among youth is not isolated behaviorally; it occurs in the context of other ongoing activities, experiences, and conflicts, and within a particular scaffold of relationships with family members, peers, and friends.

To truly determine whether SMA leads to any adverse mental health consequences, a controlled trial that randomizes youth into groups allowed to engage in SMA vs those not allowed would be needed. Obviously, such a study is impossible to do ethically and practically. Thus, we rely on data that can only approximate whether SMA is causally related to mental health problems.

The Adolescent Brain Cognitive Development (ABCD) study is a diverse, multisite, multilevel assessment cohort of 11,878 participants aged 9 to 10 years at entry that may provide such insight; the study is now in its 5th year. Given the diverse group of young participants and the longitudinal study design, it is possible to begin to examine the impact of SMA over time. However, the publicly available data are currently providing only a 2-year follow-up window and include participants aged 12 and younger, which limits the inferences one can draw currently about long-term influences of SMA.

Perhaps even more exciting, ABCD participants undergo both structural and functional magnetic resonance imaging, which—for the first time—enables determination of whether SMA affects brain development. The underlying premise is that brain structure and function are highly adaptable and change in response to the types of activities in which individuals engage. Evidence from several recent studies is consistent with the hypothesis that changes in brain structure are correlated across areas with similar function that recapitulate functional networks,¹⁴ which has been termed maturational coupling or structural correlation networks (SCNs).

Recent ABCD study data suggest that cortical surface characteristics, such as thickness or gray matter volume in youth, are organized such that they form a SCN and are related to levels of cognitive function.¹⁵ We conducted an analysis to deter-

Table. Internalizing Symptoms Associated With SMA

Depressive features	•••
Panic symptomology	•••
Delinquent behaviors	•••
Family conflict	•••
Sleep issues (eg, decreased sleep duration, increased sleep onset latency, excessive sleepiness, insomnia, and overall sleep disturbance symptom severity)	•••

mine the relationship between brain structure and SMA.¹⁶ The SMA-related latent variables were most strongly associated with visual brain structures, such that those individuals with significant exposure to activities that engage the visual system (television or video watching, gaming, and social network activities) showed structural patterns suggestive of greater maturation in the visual system (ie, thinner cortex, reduced volume, and a more complex pattern of changes in sulcal depth). We found little evidence that SMA-related brain structure differences were associated with internalizing pathology (ie, increases in anxiety, depression, or other avoidance or withdrawal behaviors).

On the other hand, those ABCD participants with thinner occipital cortices and smaller orbitofrontal volumes, as well as thinner hippocampi and smaller inferior-temporal cortical volumes, showed greater levels of externalizing psychopathology. Based on our interpretation of these findings, SMA might be problematic for some, but not all youth, and a pattern of inadequate top-down control might be contributing to this association. However, these conclusions are far from certain, and the strictly cross-sectional nature of these analyses does not permit causal inferences. Therefore, more research will be necessary to better link SMA to brain structure or function and to delineate whether such changes are beneficial or problematic.

Take-Home Messages

Given that the behavioral research findings relating SMA to mental health problems are somewhat inconsistent, mostly associative, and at an early stage, what should the take-home message be for the mental health practitioner? First, SMA is an important activity among youth; it is diverse regarding modes and methods of exposure, and technologies enabling SMA are constantly evolving. These changes in use are due in part to individual development and maturation as well as innovations in technology fields. Thus, one should assess the nature and extent of SMA use including 1) television and video watching (eg, streaming), 2) social media and related social networking activities, and 3) gaming (“On a typical day, how much time do you spend...?”). Additionally, many adolescents view pornography,¹⁷ with much viewing done on the internet, and the content of pornography on the internet has become more extreme over time.¹⁸⁻²⁰ There-

fore, it is essential that developmentally appropriate inquiries into pornography viewing should be done as part of youth assessment. Changes in SMA use should result in asking specific questions about the reasons and contexts regarding changes in modes, methods, and patterns of use.

Second, while SMA grossly assessed may have small effects on youth, individual impacts can be substantial given differences in types, patterns, and contexts of SMA consumption. Therefore, it is important to assess emotional impact and behavioral changes, and to evaluate whether changes have resulted in problems (“Have you noticed that you feel different after ...?”). Although there may be little evidence for the displacement hypothesis (ie, that SMA outcompetes other recreational activities and/or sleep) for most youth,²¹ SMA may interfere with other important activities such as school, relationships, and/or recreational activities for some individuals. As a result, gaming disorder has been introduced into the eleventh revision of the *ICD-11*. Other forms of problematic SMA may be considered as “other specified disorders due to addictive behaviors” in *ICD-11*.²²

Third, SMA can also be helpful by providing virtual support, maintaining a social network even during time of physical distancing, and yielding access to information that helps develop coping behaviors in difficult situations or honing skills (“In what way has...been helpful to you?”).

Concluding Thoughts

Assessing the evolving landscape between SMA and mental health is becoming increasingly important.²³ Taken together, a thoughtful assessment of SMA should be part of a mental assessment as much as any other aspect of social or developmental history. Only then can mental health practitioners make educated decisions about whether SMA is a friend, fiend, or both for their young patients.

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Incorporating Well-Being Into Child and Adolescent Psychiatry

» Jeff Q. Bostic, MD, EdD; Sean Pustilnik, MD; Alison Neuwirth; and Dominique Charlot-Swilley, PhD

When caring for each unique child, implementing well-being practices are an important addition to therapeutic skills. Addressing and including well-being in our efforts with children better prepares them for the future.¹ Effective well-being practices further appear to diminish vulnerability to the impacts of psychopathology,² including at the genetic level.³ While traditional child psychiatry practice focuses mainly on deficits, difficulties, diagnoses, and dysfunction, an approach centered on well-being expands assessment and treatment for the child's strengths and opportunities for positive experiences with the family.⁴ Well-being focuses on good practices for everyone, offering specific alternatives to dysfunctional patterns.

What is well-being? It encompasses multiple broad dimensions of quality of life.⁵ In addition to physical well-being, also it also includes occupational, intellectual, social, and emotional well-being (collectively, POISE). Well-being is not simply the opposite of illness, and it should be thought of on its own axis. One can have high or low symptoms of physical or mental health problems (eg, diabetes, depression), yet independently demonstrate a range of coping in the POISE domains, from struggling to flourishing. A Gallup poll of United States adults found that compared with those thriving in multiple areas of well-being, those thriving only in physical well-being missed 68% more work and were 3 times more likely to file workers' compensation claims, 5 times more likely to seek out a new employer in the next year, and more than twice as likely to change employers.⁶

Table 1. Well-Being Domains, Specific Topics, and Example Interventions

Domain	Topics	Example interventions to consider
Physical	Sleep	Cool temperature; light for sleeping; soothing lavender/vanilla smells; reduced evening screen time; bedtime routine
	Nutrition	Focus on breakfast (smoothies); family meal times
	Activity	7000+ steps; nonsedentary habits; stretches/yoga
	Music	Daily music as part of routines; creation of playlists
Occupational	Equity	Fair treatment; respect for all others
	Time management	Sustaining focus/timer; scheduling; eliminating distractions; overcoming procrastination
	Manages adversities	Resilience skills; addressing systemic obstacles
	Teamwork	Helping others; sharing efforts with others
Intellectual	Reading	Keep books with you; discuss them with friend(s); explore book club/library opportunities; podcasts
	Watching	Lists of classic films; film clubs; shared > personal screen
	Exploring	Brain games; hiking/walking/observing; nature (birds/trees)
Social	Positive friend traits	Maintaining integrity/avoiding lying and gossip; caring; congeniality/humor; schedule social time
	Active listening	Listening; conversing; nonverbal communication
Emotional	Coping with stress	Healthy alternatives; reframing; problem-solving; social support; mindfulness/meditation (apps such as Calm and Headspace)
	Using thrive and survive emotions	Recognizing and responding to both positive (thrive) and negative (survive) emotions

Applications in Practice

We have devised an efficient instrument we have devised over the past 4 years to assess these POISE domains of well-being for children in a clinical setting, which is freely available for use at www.medstarwise.org/POISE (see: Well-Being Assessment Measure: Child/Adolescent version). Adolescents can complete this form themselves; parents may complete it for younger children.

This measure allows clinicians and families to rapidly identify both general domains of strength and weakness, and to recognize specific topics to address within each domain. The clinician can then include well-being within the treatment plan. For example, a low rating in the sleep item, despite stable scores in all other physical domain items, illuminates a target for intervention. **Table 1** shows the well-being interventions to consider for topics within these domains.

Creating a Well-Being Plan

Several factors can guide providers as they select and prioritize well-being practices for each patient. First, what matters most to this individual and family? More salient and important goals usually take priority. Second, cultural factors influence well-being, including the values, tasks, and aspirations of each well-being domain. Cultural influences shape how different individuals care for their bodies, manage emotions, and choose relationships, and thus guide individual well-being practices and goals. Third, developmental attunement for each individual remains important; interventions for intellectual stimulation will change across the age span, along with age-appropriate skills for physical activity, time management, emotional regulation, and social skills and relationships.

Motivational interviewing approaches are helpful for youth and families to determine whether they are invested in making a change to achieve a goal.⁷ Usually a small number of goals (1 or 2) agreed upon by the child and parent, and even shared with others, are easiest to accomplish.

Clinical Case Application

“Samantha,” a 14-year-old female, described symptoms consistent with depression. When completing the POISE scale, she described an inability to fall and remain asleep, then being inactive throughout the day; trying to lose weight by switching to diet sodas; and struggling to get going. At school, Samantha was irritable with staff and was not turning work in on time, and she felt her school was isolating for students with mental health issues. She felt like others were talking about her in the cafeteria and feared that she had few peers who understood her. Samantha could not understand why she felt so sad, and she reported screaming at others who spoke to her.

In addition to treatment for her depressive symptoms, which might include cognitive behavioral and/or antidepressant treatment, well-being practices may also be helpful to alter Samantha’s current routine as well as her future.⁸

In this case, a well-being plan might address all of the POISE domains with interventions preferred by Samantha. For example, in the physical domain, she might be receptive to making changes to her bedtime routine to improve her sleep, to alter her food/drink choices, to increase daily walking, and to create music playlists to make walking more enjoyable. Samantha might initially prioritize 1 or 2 goals, such as “I will walk 5000 steps per day for the next 2 weeks, and monitor my en-

ergy level and mood each day,” or “I will replace soda with tea and fruit-flavored waters for 1 week, and monitor the impact on my sleep and appetite.” She could similarly use these POISE domains to identify other subsequent priorities and goals for her health plan. Usually, 1 or 2 goals at a time is preferable so the patient can focus on making these routine well-being behaviors.

Often mood symptoms are a priority for child psychiatrists, and replacing unhelpful behaviors is a vital component of treatment. **Table 2** shows a simple approach for youth when they are feeling overwhelmed or employing unhealthy behaviors. In Samantha’s case, identifying specific responses she has, then challenging them with Healthy Alternatives/Reframing/Problem-Solving/Social Supports options, may prepare her with concrete well-being practices to replace these behaviors.

Concluding Thoughts

Not only can well-being interventions be useful adjuvants to specific treatments for patients’ psychiatric symptoms, but they can also help youth address their unique constellation of symptoms and ingrain healthy practices to enhance their quality of life in multiple domains. The lists of preferred and richer evidence-based strategies will continue to grow, so that ongoing recognition and consideration of well-being can become an effective addition to our care of youth.

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Table 2. Using HARPS To Replace Unhealthy Responses

Healthy responses	Unhealthy responses
Find healthy alternative activities: <ul style="list-style-type: none"> ▪ Exercise, take a walk ▪ Listen to music ▪ Read or journal ▪ Meditate 	<ul style="list-style-type: none"> ▪ Deny/act as though the experience never occurred ▪ Use substances that dull senses
Reframe the experience: <ul style="list-style-type: none"> ▪ Consider how this experience affects me. ▪ How can I accept this situation? ▪ What did I learn from this experience? ▪ Reflect (Why is this on my path?) 	<ul style="list-style-type: none"> ▪ Focus on how unfair this is to you, that you do not deserve this, and that the world is against you personally
Initiate problem-solving: <ul style="list-style-type: none"> ▪ How can I respond differently? ▪ What parts of this situation can I change? 	<ul style="list-style-type: none"> ▪ Avoid this circumstance, or anything like it, in the future ▪ Do not think through options; just ignore this circumstance
Social support: <ul style="list-style-type: none"> ▪ Ask: How do others see/describe this? ▪ Can others give me a reality check? ▪ Are there others who might have useful input? ▪ Can I partner with others to manage this? 	<ul style="list-style-type: none"> ▪ Find others to vent to, and who will agree with you no matter what, and with whom you can complain about your situation

HARPS, Healthy Alternatives/Reframing/Problem-Solving/Social Supports

Facilitating Autism Diagnosis

» Andrew J. Schuman, MD

Clinicians generally screen children for autism spectrum disorder (ASD) twice, at ages 18 months and 2 years, during routine health maintenance exams. Unfortunately, this neurodevelopmental condition often evades formal diagnosis until a child is 4 years or older.^{1,2} To expedite diagnosis, investigators are exploring a variety of artificial intelligence (AI)-based diagnostic systems as well as telehealth- and sensor-based technologies.

Diagnostic Issues

ASD affects 1 in 59 children in the United States.³ In many circumstances, a child suspected of having ASD is referred to a multidisciplinary diagnostic team composed of multiple medical and non-medical specialists. Thus, there are often lengthy wait times for an evaluation. If a child does not meet threshold criteria, the assessment is considered inconclusive and parents must wait until the child is older for repeat assessment.

Many factors may delay the diagnosis. Individuals in poor communities and members of racial minority groups often have limited access to the services.⁴ In addition, only 60% of pediatricians nationwide screen children for developmental delays despite American Academy of Pediatrics (AAP) recommendations to perform screens at 18- and 24-month wellness checks. Also, screening may not result in appropriate follow-up care. In one study, for example, only two-thirds of those who failed screening were referred for a diagnostic ASD evaluation.^{5,6} The screening tools themselves present challenges. For instance, it has been shown that the Modified Checklist for Autism in Toddlers – Revised with Follow-up (M-CHAT-R/F) has a sensitivity as low as 39% in detecting children with ASD.⁷ Lastly, the COVID-19 pandemic has resulted in significant delays in evaluations.

Many tools are available to screen for ASD, including the Ages and Stages Questionnaires, the Communication and Symbolic Behavior Scales, the Parents Evaluation of Developmental Status, the Screening Tool for Autism in Toddlers and Young Children, and the aforementioned M-CHAT-R/F (Table). Pediatricians often use M-CHAT-R/F at ages 18 months and 24 months; it queries parents regarding their child's perception of others, use of gestures, and interactive eye contact, as well as vocal communication and their ability to interact with parents and children. The AAP recommends referral for a diagnostic evaluation when children screen positive or if the pediatrician is suspicious of the diagnosis.

The DSM-5 consolidated previous categories of ASD into 1. To meet ASD criteria, a child must have 3 of 3 symptoms relating to social communication and interaction, plus 2 of 4 symptoms relating to repetitive or restricted behaviors (Figure).⁸

This recharacterization and simplification of the elements needed for ASD diagnosis has facilitated

Figure. ASD Diagnostic Criteria According to DSM-5⁸

PERSISTENT SYMPTOMS OF SOCIAL COMMUNICATION AND INTERACTION.

Currently or by history
All 3 symptoms are required:

1. Deficits in social-emotional reciprocity. Children manifest a failure of normal back-and-forth conversation, reduced sharing of interests or emotions, as well as failure to respond to social interactions.
2. Deficits in nonverbal communication behaviors. Children demonstrate poor integration of verbal/nonverbal communication, have irregularities in eye contact/body language, and deficits in the use of gestures.
3. Deficits in maintaining and understanding relationships. Children demonstrate a lack of interest in peers, sharing imaginative play, or making friends.

SYMPTOMS OF REPETITIVE OR RESTRICTIVE BEHAVIORS.

Currently or by history.
Two of 4 required:

1. Stereotyped or repetitive motor movements, use of objects or speech (eg, idiosyncratic phrases, lining up toys, etc).
2. Insistence on sameness, ritualized nonverbal or verbal behaviors (eg, distress at small changes, difficulties with transitions, etc).
3. Fixated interests that are abnormally intense (eg, strong attachment to objects).
4. Hyper- or hyporeactivity to sensory inputs or unusual interest in sensory aspects of the environment (eg, indifference to pain, adverse response to sounds or textures, fascination with lights or movement).

tated its diagnosis by specialists. Many use a chart similar to the Figure as an intake screening form before proceeding with a diagnostic evaluation.

The Autism Diagnostic Observation Schedule (ADOS) test and/or the Autism Diagnostic Interview – Revised (ADI-R) can also be used to evaluate for a suspected diagnosis. The ADOS is an observational play and activity assessment that takes up to an hour to complete, while the ADI-R is a 93-point questionnaire that may take several hours to complete.⁹ Many developmental pediatricians and child psychologists utilize their own screening methods rather than performing a full ADOS or ADI-R, sometimes using such screening tools as the Social Responsive Scale and the Childhood Autism Rating Scale. Most importantly, although these tools help with diagnosis, ASD is a

clinical diagnosis best rendered by clinicians with the training and expertise to do so.

Technologies Using Sensors

Children affected with ASD are a heterogeneous group, with varying degrees of functional limitations. Many have comorbidities that include seizures, attention-deficit/hyperactivity disorder, oppositional defiant disorders, sleep disorders, speech delay, and others. Researchers have long looked to sensor-based technologies, many employing AI algorithms, to screen for children with ASD. AI is particularly useful for identifying patterns within data, and it therefore can be advantageous in identifying markers associated with an ASD diagnosis. AI algorithms are only as good as the training datasets inputted into a diagnostic system, but they do have the potential to improve medical care.¹⁰

Although a complete discussion of sensor technologies is beyond the scope of this article, investigators have had some promising results using sensors to analyze facial expressions, vocalizations, touch sensitivity, eye tracking, movements, and interactions with robots—all of which may help identify children with ASD. Unfortunately, to date, none of these technologies have been proven to be sensitive enough to be used diagnostically.¹¹

DTx-Based Tools

Developed over several years with National Institutes of Health grant funding, the Naturalistic Observation Diagnostic Assessment (NODA) was developed by Behavior Imaging Solutions. This is a digital therapeutic (DTx) that can facilitate the diagnosis of ASD, and it has 2 components. Parents use a smartphone-based application to complete a developmental questionnaire and to record and upload 10-minute videos of their child. NODA scenarios include the child playing alone, the child playing with others, a family mealtime, and a behavior of parental concern.

The web-based portal allows the clinician to analyze submitted videos for features of ASD. The doctor then completes a DSM-5 ASD checklist and considers the diagnosis. The results of several studies have indicated that the BSI system is easy to use and renders diagnoses comparable with those produced by a traditional ADOS evaluation.^{12,13} For example, a 2017 study compared the diagnostic accuracy of the NODA system with in-person evaluations by experienced ASD diagnosticians for 40 families who were seeking an ASD evaluation and 11 families with normally developing children. The diagnostic clinicians were blinded as to which group they were evaluating and used ADOS, ADI-R, or other diagnostic tools to render a determination of ASD status for each child. Sensitivity between NODA and the in-person exam was 85%, and the specificity was 94%.¹⁴

The developer is currently in the process of integrating AI into NODA, using vision algorithms to tag video frames containing suspect diagnostic features. This AI is expected to be incorporated

Table. Screening and Diagnostic Tools Used in ASD Diagnosis¹⁹

AGES AND STAGES QUESTIONNAIRES

Parent-completed questionnaire; series of 19 age-specific questionnaires screening communication, gross motor, fine motor, problem-solving, and personal adaptive skills; results in a pass/fail score for domains.

COMMUNICATION AND SYMBOLIC BEHAVIOR SCALES

Standardized tool for screening of communication and symbolic abilities up to the 24-month level; the Infant/Toddler Checklist is a 1-page, parent-completed screening tool.

PARENTS EVALUATION OF DEVELOPMENTAL STATUS

Parent interview form; screens for developmental and behavioral problems needing further evaluation; single response form used for all ages; may be useful as a surveillance tool.

SCREENING TOOL FOR AUTISM IN TODDLERS AND YOUNG CHILDREN

Interactive screening tool designed for children when developmental concerns are suspected; consists of 12 activities assessing play, communication, and imitation skills; takes 20 minutes to administer.

MODIFIED CHECKLIST FOR AUTISM IN TODDLERS - REVISED WITH FOLLOW-UP

Parent-completed questionnaire designed to identify children at risk for autism in the general population.

AUTISM DIAGNOSIS INTERVIEW - REVISED

Diagnostic instrument focuses on behavior in 3 main areas: reciprocal social interaction; communication and language; and restricted and repetitive, stereotyped interests and behaviors. Appropriate for children with mental ages about 18 months and above.

AUTISM DIAGNOSTIC OBSERVATION SCHEDULE - GENERIC

Semi-structured, standardized assessment of social interaction, communication, play, and imaginative use of materials. Observational schedule consists of four 30-minute modules.

CHILDHOOD AUTISM RATING SCALE

Brief assessment for use with a child 2 years or older. Includes items drawn from 5 prominent systems for diagnosing autism; each item covers a particular characteristic, ability, or behavior.

GILLIAM AUTISM RATING SCALE - SECOND EDITION

Assists teachers, parents, and clinicians in identifying and diagnosing autism and its severity in individuals aged 3 through 22 years.

DSM-5

Provides standardized criteria to help diagnose ASD.

into the portal over the next 2 years and will speed the diagnostic process.

As with many DTx, the ease of use and availability of this system can shorten wait times to diagnosis considerably. Best of all, the evaluation can be done remotely, even in a pandemic, and the specialist can render a diagnosis expediting appropriate interventions for the child with ASD.

A Promising ASD Diagnostic

Another possibility is using a multimodal AI-based system to diagnose ASD.^{15,16} The prescription-only system developed by Cognoa, called Canvas Dx, was granted breakthrough device status via a preliminary submission to the US Food and Drug Administration (FDA), and it recently received FDA authorization.¹⁷

Cognoa AI software was trained on datasets that were compiled from ADOS and ADI-R score sheets of children aged between 18 and 84 months, supplied by numerous ASD evaluation and treatment centers. Cognoa's system includes: 1) a parental questionnaire; 2) a questionnaire filled out by the patient's pediatrician; and 3) an analysis of 2 to 3 uploaded short videos, each 1 to 2 minutes long, of the child during mealtime or play at home. The videos are analyzed and scored by trained analysts for features of ASD who respond to a behavior questionnaire. AI algorithms analyze the questionnaires and video report and render a decision regarding whether the child has or does not have ASD, or if the valuation is inconclusive.

Study results validated Cognoa's system; 375 sample patients evaluated over 2 years, indicating that the system could identify children with ASD with sensitivity and specificity as high as 90% and 83%, respectively.¹⁸

More recently, the company completed a double-blind clinical trial at 14 sites around the United States, utilizing an improved algorithm to gather data. The trial involved 425 participants aged between 18 and 72 months whose parents or doctors expressed concern about their development but had not previously been evaluated for ASD. Each child was assessed twice: once using Cognoa's diagnostic, and once by a specialist clinician based on DSM-5 criteria. The study ran from July 2019 through May 2020, so some of the children were evaluated remotely during the pandemic via telemedicine. According to the company, the tool performed equally well when administered remotely and showed that Cognoa's diagnostic is highly accurate across males and females as well as ethnic and racial backgrounds.

Concluding Thoughts

The diagnosis of ASD remains a challenge, and recent advances in technology may expedite the identification of affected children so the child can receive early interventions. Looking ahead, various smart device-based applications are either in development or will soon be available to

assist parents in socializing ASD children. Progress is being made, and soon parents and providers will leverage technologic advances to better identify ASD.

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The ABCs of Vaping

» Catherine W. Striley, PhD, MSW, MPE; and Sara Nuttey, MS

The word *vaping* can be deceptive, since the single word can represent different behaviors. Vaping refers to a method of substance inhalation that delivers anything from blueberry-flavored vitamin D to delta-9-tetrahydrocannabinol (THC) into the body. Although health professionals often refer to electronic cigarettes (e-cigarettes) and vaping synonymously, e-cigarettes represent only a small fraction of the growing market for vaping products available to consumers of all ages.

Why All the Fuss?

We know that breathing in tar and asbestos is risky, but what about zinc, lead, chromium, manganese, and copper? All have been identified as components of various vaping products (eg, e-liquids, vape juice), although the long-term health consequences of these ingredients are not well defined. Although some e-liquid ingredients are considered to be safe to be ingested and processed in the gut

and may thus be benign in that regard (eg, vegetable glycerin and propylene glycol), they may cause harm in the lungs.² And, beyond the lung damage it can cause, aerosol inhalation may increase cardiovascular risk.³

In addition, nicotine vaping products increase the risk for the same health consequences as any other nicotine exposures, including: subsequent development of a nicotine addiction; priming for use of other substances; changes in attention, cognition, and impulse control; and increased risk of developing mood disorders.² The risk is compounded by the ready availability of vape juices and e-liquids that have high concentrations of nicotine, beyond what are found in traditional tobacco products.⁴

Young children and developing fetuses may also be prone to indirect health consequences of vaping products. For instance, there are reports of vaping liquids being swallowed and absorbed through the skin and eyes in young children, resulting in poisoning. Fetal exposure can result in multiple adverse health consequences, including sudden infant death syndrome.³

So Why Vape?

Given the potential for harm, why do individuals vape nicotine and other harmful chemicals for purposes other than smoking cessation? Among youth, curiosity is the most common reason for vaping.⁵ Vaping may be seen an act that brings social benefit: Friends use what their friends use.⁶ Available online and in neighborhood stores, vaping products may be perceived as both fashionable and convenient.⁵ Plus, vape systems can be discreet (ie, no visible aerosol) or flashy (ie, production of large vape clouds). With advanced features such as voice control, accent lighting, and Bluetooth compatibility, there is a vaping device to appeal to almost any subculture and customer.

The ability to customize vape systems and liquids carries additional risks. Most samples obtained from the e-cigarette liquid of individuals being treated for e-cigarette or vaping product use-associated lung injury (EVALI) contained THC. Vitamin E

acetate was identified in all samples, and glycerin, propylene glycol, diacetyl, aldehydes, formaldehyde, terpenes, organic compounds, and trace metals may have contributed to the more than 2800 EVALI cases and 68 associated deaths.^{7,8} In our investigation of college students' vaping data collected from the 2018 to 2019 Health Minds Study survey, we found that almost 1 in 4 students who vaped used THC,⁹ and an analysis of 2018 National Youth Tobacco Survey data found that about 1 in 4 of the middle and high school student sample had vaped marijuana.¹⁰

Is This Behavior Legal?

The short answer is yes. A few US states and tribal governments, and some countries, have broadened prohibitions against smoking in public places to include vaping, but most have not. The US Food and Drug Administration (FDA) regulates flavors, predominantly when marketed to children and youth and when sold without age verification or without limiting number.¹¹ Menthol, previously considered an adult flavor, is now banned per the FDA.¹²

How About Smoking Cessation?

Although vaping products are being used by non-smokers, vaping has utility as a smoking cessation aid for adult consumers.^{13,14} Given the undeniable harms of smoking, vaping provides an option for people who are ready to quit smoking.^{13,14}

Among youth, however, vaping is more often initiated as an addition or gateway to smoking. According to the results of one study, only 7.3% of high school seniors who vaped did so for smoking cessation.¹⁵ Furthermore, individuals with dual use (smoking and vaping) are exposed to increased harms.¹⁶

Clinical Implications

“Paul,” aged 35 with no history of psychiatric disorders, was a smoker for more than 30 years. Despite his use of numerous quit methods, Paul's frequent attempts to stop smoking were curtailed by his anxiety and disrupted concentration. Finally, his primary care provider convinced him to give vaping a 2-week try. Although cynical at first, Paul was relieved when he discovered vaping worked for him. In addition, he was thrilled to find products that were within his budget.

Unfortunately, vaping was not a 100% panacea. One day while working at his computer, Paul felt a sudden flash of pain and his pant leg burst into fire. A visit to the emergency department and a skin graft were required after his battery exploded in his pocket. Nevertheless, he is still vaping.

Paul says he will never return to



Table. Assessing Vaping Behavior and Intentions to Quit

Substance vaped	Vape juices and e-liquids may include nicotine, delta-9-tetrahydrocannabinol, vitamin infusions, and other flavors. Clients should be asked about use of multiple products/substances and products most frequently inhaled.
Dosage	Ask about the number and type of cartridges used each day/week/month or the number/duration of puffs at each use.
Frequency	Ascertain how often patients use their vape device.
Dual use	Research in dual use (engaging in both e-cigarette and combustible cigarette use) is limited, but it may reflect higher levels of nicotine dependence. ²⁸ Assessment of dual use and use patterns (ie, simultaneously, subsequently, distinctly) is advised.
Use disorder	As with any substance, assessment for potential tobacco or cannabis (or other drug) use disorder is needed. If using a screening from DSM-IV rather than DSM-5, craving should be addressed.
Motivation to use	Motivational domains for initiation and cessation may include, but are not limited to, relationships/social, physical, emotional/psychological, self-concept/image maintenance, financial, health.
Motivations to quit	

smoking cigarettes, although he misses it. He is scheduled to see a pulmonologist; he is certain that vaping has been better for his health than the 2 packs a day he used to smoke. However, family and friends are concerned, he reports. They have pointed out that he is never without his vape pen, and he has realized he uses it with no conscious knowledge of doing so, regardless of where he is.

ASSESSING THE CLINICAL SIGNIFICANCE OF VAPING. Talking to a patient about vaping may require some investigation (Table). Frequency of use and the types of products used influence the safety and clinical significance of the behavior. If the patient is distressed by their behavior, experiences functional impairment, or reports poor health outcomes including symptoms of tobacco or cannabis use disorders, you may decide to provide assistance and help your client quit, or reduce, vaping behavior.

RESOURCES TO HELP YOUR PATIENT QUIT VAPING. The US Department of Health and Human Services^{17,18} and the FDA¹⁹ have online and printed resources to assist with smoking cessation, as have most US states.²⁰ In-person and online classes and/or support groups, tailored text messaging services, a free QuitGuide app, and information related to nicotine replacement products are available. Patients can consult and access these resources when they want to quit smoking or vaping. While vaping cessation research is scant²¹⁻²³ and is primarily limited to nicotine vaping, methods used to quit are likely amenable to those used in smoking cessation.¹⁶ US Preventive Services Task Force recommendations for clinicians are to ask about use, advise quitting, and provide behavioral interventions and pharmacotherapy.²⁴

SPECIAL POPULATIONS. Teens and adolescents may require niched interventions, whether they are consuming nicotine via vaping or other methods.²¹⁻²³ To this end, the Truth Initiative²⁵ funded the development of a text-to-quit mobile application as an addition to their quit program for teens. This pro-

gram is based on research of vaping patterns, quit attempts, and cessation motivation; interventions should be tailored to address social influences, outcome expectancies, and intentions to quit.²¹ Women who are pregnant also need a tailored approach to quit vaping; counseling techniques, including relaxation activities,²⁶ and monetary incentives improve outcomes.²⁷ Nicotine replacement therapy may also be helpful.²⁸

Dr Striley is an associate professor and director of psychiatric epidemiology at the University of Florida. **Ms Nuttey** is a PhD student in epidemiology at the University of Florida.

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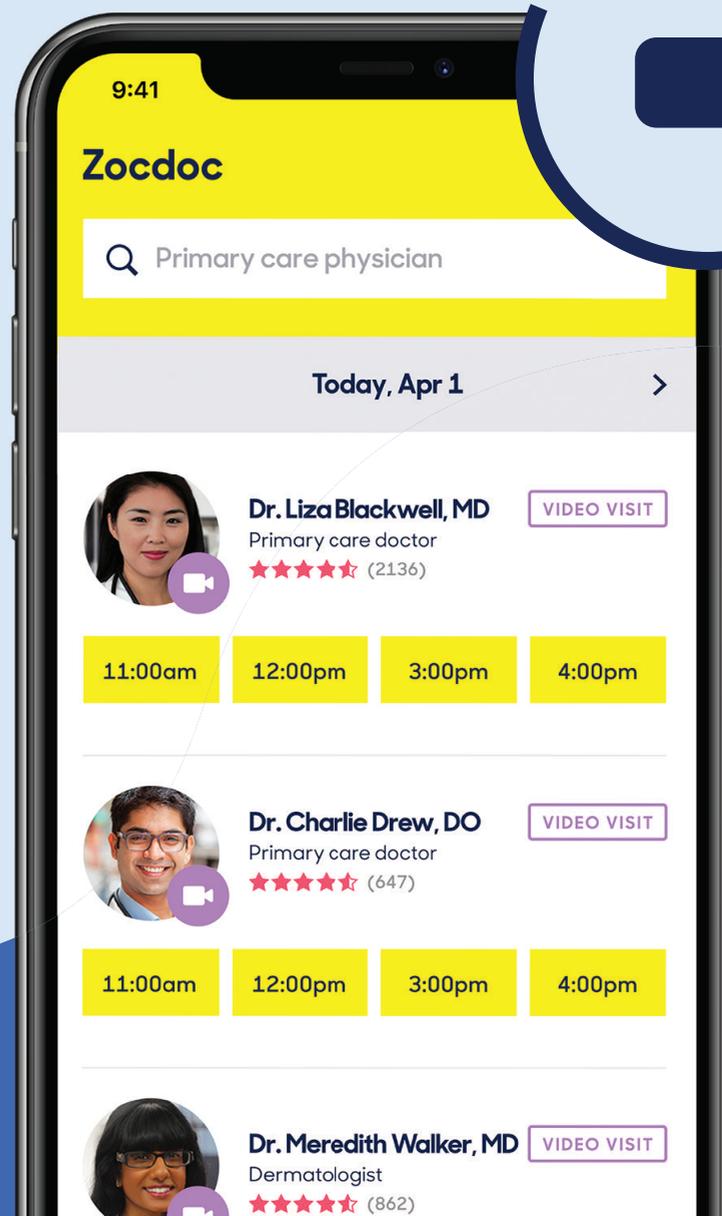
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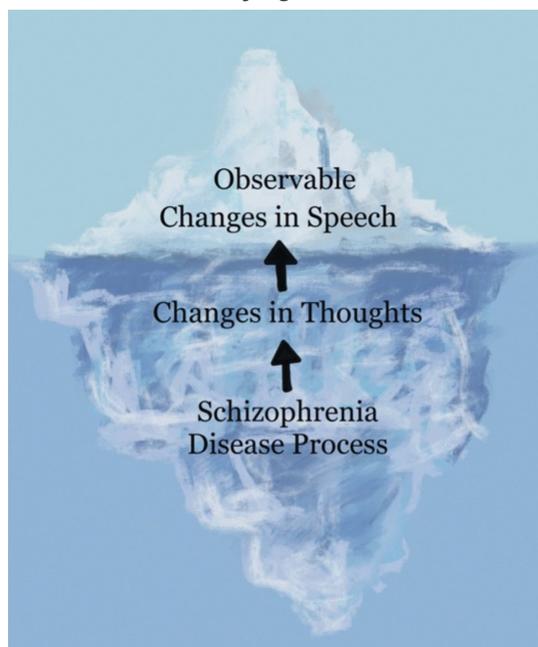
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Table. Acoustic and Lexical Measures in Relation to Speech Disturbance in Schizophrenia

Speech feature	Category	Description	Clinical correlate
Word count	Lexical	<ul style="list-style-type: none"> Number of words per sentence, per minute, or per sample Number of sentences per sample 	<ul style="list-style-type: none"> Poverty of speech Alogia
Uniqueness of words	Lexical	Ratio of unique words to total words	<ul style="list-style-type: none"> Poverty of content of speech Decreased ideational richness
Speech errors	Lexical	Number of incomplete words, repetitions, restarts, pauses filled with “um” and “uh”	<ul style="list-style-type: none"> Dysfluency Aphasia
Coherence	Lexical	<ul style="list-style-type: none"> Words and phrases are assigned vectors that represent their meaning The distance between ideas is calculated 	<ul style="list-style-type: none"> Derailment, flight of ideas Loose associations Tangentiality Incoherence
Parts of speech	Lexical	<ul style="list-style-type: none"> Counts of pronouns (eg, first-person I, we; second-person you, your) Nouns Adjectives Determiners (eg, this, a, some) 	<ul style="list-style-type: none"> Increased self-reference (first-person singular pronouns) Impaired theory of mind Decreased ideational richness
<ul style="list-style-type: none"> Pitch variability Vocal qualities 	Acoustic	<ul style="list-style-type: none"> Changes in fundamental frequency (pitch) Frequency of waveforms for volume and pitch 	<ul style="list-style-type: none"> Decreased vocal inflection Aprosody
<ul style="list-style-type: none"> Pause length Pause duration 	Acoustic	<ul style="list-style-type: none"> Length of pauses Number of pauses 	<ul style="list-style-type: none"> Latency Poverty of speech

phrenia spectrum disorders from that of comparison participants without schizophrenia.¹¹ The TLC scale was used to rate positive and negative thought disorder symptoms. Then, we used NLP methods to extract lexical information on multiple levels: individual words, parts of speech (eg, nouns, adverbs, adjectives, etc), and sentence-to-sentence coherence. When classifying participants into either the schizophrenia or health comparison group, we found machine learning algorithms performed significantly better using NLP-derived features (87% accuracy) than clinical ratings (68% accuracy), suggesting that important information is being captured

Figure 2. Speech Is the Observable Reflection of Underlying Disease Processes



by NLP. In addition, we found preliminary evidence that individuals with schizophrenia are much more likely to speak partial words (eg, “I went to th- the store” or “I guess we sho-... Let’s go out”), which has not been reported previously to our knowledge.

In another study, we combined acoustic and lexical speech features in machine learning models to predict separate items from the TLC.¹² Importantly, we noted that speech disturbance in schizophrenia is likely multifaceted, and it should not be treated as a single uniform entity.

The Future of Speech Biomarkers

Based on their ability to measure thoughts in an automated, fast, objective, and inexpensive manner, speech biomarkers could fundamentally alter clinical psychiatric practice. As illustrated in **Figure 2**, speech can be considered the visible extension of the changes in thought and brain circuitry that are at the core of schizophrenia. By mapping these connections, and leveraging the power of artificial intelligence and human language processing technology, I believe that we will develop a way to use language to scan the brain and offer personalized medicine.

Imagine a patient walking into an intake appointment and describing their experiences and circumstances. The psychiatrist hands the patient a tablet, which leads them through some brief speaking tasks. A spinning wheel appears for a few seconds, followed by numbers and graphs that reflect their symptoms and their related brain circuitry correlates. This brings up a menu that includes recommended digital therapeutics, pharmacology, and psychotherapy, and offers ways to track progress and to warn of relapses be-

fore they occur. The scenario would not be very different from checking cancer markers in oncology, autoantibodies in rheumatology, or myriad existing paradigms in other medical fields.

Already, early evidence suggests that speech biomarkers reflect underlying changes in the brain. In work by Palaniyappan et al on the speech of individuals with mania or schizophrenia, decreased cohesiveness between concepts was significantly correlated with measures of resting state brain connectivity and gyrification (folding patterns of the brain).¹³ Perhaps, with additional research, we will be able to link specific speech markers to changes in specific circuits.

Looking Forward

It is important to remember that our mission is the healing and well-being of individuals and families. This is not technology for the sake of novelty, no matter how nifty the gadget. Finally, the availability of brain measures should not mandate reliance on pharmacology over psychosocial interventions—quite the opposite. Automated language processing can be harnessed to measure changes in thought and brain structure on a personalized level. This layer of technology should not occlude the individual but rather allow clinicians to delve deeper into each unique case.

Dr Tang is an assistant professor of psychiatry at the Feinstein Institutes for Medical Research and the Donald and Barbara Zucker School of Medicine at Hofstra/Northwell. She is the cofounder and chief science officer of North Shore Therapeutics. Disclosures: Dr Tang serves as a consultant for Winterlight Labs.

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TALES FROM THE CLINIC: THE ART OF PSYCHIATRY

SERIES EDITOR NIDAL MOUKADDAM, MD, PHD

“I’m Not Ready to Die”

» Hai Le, MD; Sawsan Khan, MD

In this installment of *Tales of the Clinic: The Art of Psychiatry*, we follow a psycho-oncology case of lung cancer, compounded by depressive and anxiety symptoms. Faced with fear of death, individuals go through stages of grief, as described by Elisabeth Kübler-Ross, MD, in 1969. This discussion highlights the psychotherapeutic, pharmacological, and diagnostic considerations of this comorbidity.

CASE STUDY

“Mr Arnold” is a 67-year-old retired teacher with no past psychiatric or medical history. He was referred to a psychiatry clinic for sadness and anxiety shortly after being diagnosed with metastatic adenocarcinoma of the lower lobe of the left lung. The devastating diagnosis caught Mr Arnold off guard just months into his retirement, as the only symptoms he experienced were cough and progressive fatigue. Besides these complaints, he had no past medical issues, always stayed committed to a healthy lifestyle, and underwent regular screenings and physical exams. Mr Arnold did not have any history of tobacco smoking, alcohol drinking, or any other substance use. He felt numb when he first heard the diagnosis because he was overwhelmed with a range of strong emotions: disbelief, anger, fear, anxiety, and sadness. Mr Arnold’s retirement plan now had to be put on hold so he could focus on cancer treatment. He had already suffered tremendous grief a few years earlier after the loss of his wife of 30 years to cancer. This time, he was traumatized by cancer as a firsthand experience.

During the initial visit to the psychiatry clinic, he complained predominantly of fear of death, hopelessness, insomnia, social isolation, anger, guilt, and worry for his girlfriend if the treatment fails: “What will she do without me? Who will take care of her after I die?” Mirtazapine was started to target depression, anxiety, poor sleep, and low appetite; however, Mr Arnold found the medication too sedating. Sertraline was subsequently started and was much more tolerable and helpful with alleviation of anxiety and depression.

He was started on chemotherapy and radiation treatment soon after diagnosis. During the early stages of cancer treatment, he had difficulty coping with the treatment burden and reported worsening symptoms of anxiety. He was affected not only by the cancer diagnosis, but also by the treatment and its side effects, which worsened his depression and anxiety, lowered his quality of life, and exacerbated his loneliness and social isolation. Besides pharmacological intervention for depression and anxiety, he was concurrently seen by a psychotherapist to work on relaxation techniques, deep breathing exercises, and cognitive behavioral therapy. After persevering through almost 2 years of cancer treatment, Mr Arnold felt extremely relieved when the PET scan showed no evidence of active disease. Subsequent CT scans were negative as well. Mr Arnold later continued maintenance oral chemotherapy. While he felt relieved and hopeful for the future, a part of him still felt anxious that the cancer might recur.

Arnold found himself in shock (the denial/shock stages of grief). He now had to face the dreadful transition from anticipating years with joyful activities to navigating the uncharted waters of a deadly illness and difficult treatment. Mr Arnold experienced demoralization similar to Erik Erikson’s concept of despair in the final stage of one’s life, where he partially felt regret over the life he had lived and the feeling of hopelessness.

Compared to other malignancies, lung cancer is associated with a higher rate of mortality and symptom burden, which can cause serious psychological suffering. Facing a terminal illness, Mr Arnold felt devastated and in despair; he now believed he had only a slim chance of being able to do the meaningful things that he had worked and planned for all his life (ie, traveling around the world). Although he reflected on the life he had lived with pride, having raised 2 successful children, he felt regret for not doing enough of what he felt would have brought him happiness (the depression stage of grief). During the course of his cancer treatment, Mr Arnold constantly found himself in a tug of war between hope for a full recovery (so he could travel) and, in his words, “make peace” (achieving ego integrity, the bargaining stage of grief) with the life that he had led and the fear of death.

Reflecting on his life, Mr Arnold felt that being diagnosed with lung cancer was unfair for him since he never had medical problems and had been committed to a healthy lifestyle (the anger stage of grief). He never smoked tobacco, drank alcohol, or abused any substance. Like most lung cancer patients, Mr Arnold was diagnosed when the cancer was in the late stage because his early symptoms—dry cough and fatigue—were nonspecific and dismissed without further work-up. He also reported feeling guilty about the possibility of becoming a burden on his girlfriend, who herself had chronic conditions. Self-compassion is key in improving outcome at this stage in treatment.¹ In aging patients, this is a common concern that needs to be addressed in multimodal treatment planning, as there is increasing recognition that caregiver health and patient health are interdependent.²

During his first visit with psychiatry, Mr Arnold reiterated tearfully that he had saved money all his life for retirement and planned to travel extensively in the last meaningful years of his life. The addition of psychotherapy was essential in guiding the patient through the stages of grief. Although lung cancer is the most frequently occurring cancer and the leading cause of cancer death in men,³ it is essential to help patients realize that many cancer occurrences do not lead to death (the acceptance stage of

The Stages of Grief

Lung cancer is second only to breast cancer in prevalence. Older adults with lung cancer face a range of challenging issues, including demoralization, isolation, treatment distress, anxiety, and depression. Some issues relate to loss of control and dignity, whereas others stem from problems related to quality of life. Smokers, or individuals who feel their cancer stemmed from negative behaviors of their own doing, often experience shame

and worse depression.¹ In therapy, fear of mortality and psychosocial decline need to be addressed. Stages of grief must also be highlighted and worked through, although stages do not have to occur in clean, predictable order.

For Mr Arnold, it was hard to imagine a worse time for him to receive the news of this devastating diagnosis because, after decades of working hard, he had been looking forward to spending the post-retirement years traveling. Like other patients, Mr

grief). He was psychologically tormented by the constant fear of death, especially in the aftermath of the diagnosis and early stages of treatment.

As the lung cancer treatment progressed, Mr Arnold started to worry more about his financial situation since his retirement savings were quickly depleted by medical bills. He felt resentful that a significant portion of his retirement savings was now drained, and he could not help his girlfriend. Alleviating the burden of treatment in this situation was integral to improving the patient's anxiety and depression. Considerations for patients in this situation include aggression of disease/cancer staging, likelihood of poor prognosis, and uncertainty in treatment and outcome.

Pharmacological Considerations

Screening for depression among patients with lung cancer can be tricky as multiple confounding factors present as neurovegetative symptoms, mostly related to the cancer and its treatment; for example, low energy, poor appetite, decreased motivation, loss of interest, and decreased concentration. Research has shown that the level of distress experienced by lung cancer patients is not correlated with the type or stage of cancer, but that individuals with depression and cancer may have higher health resource utilization and worse outcomes.⁴

The best management of lung cancer and treatment distress requires early and comprehensive care coordination involving a multidisciplinary team to address physical suffering, spiritual needs, psychosocial stressors, nutritional needs, and psychological suffering. The goal is to provide adequate control of physical symptoms, psychosocial support, and management of anxiety and depression.⁵

Here, Mr Arnold started taking mirtazapine for depression; the medication was also helpful for anxiety. Another benefit of this antidepressant, and the reason it was selected as first line, is that it alleviates gastrointestinal symptoms (nausea) induced by chemotherapy and poor sleep related to distress and anxiety. Mr Arnold had a good response to mirtazapine; however, the sedation caused by its side effect was a major issue because he already struggled with fatigue and low energy. Sertraline was later started and proved to be a better choice for his depressive symptoms. However, in treating patients with cancer, drug interactions

have to be carefully considered because selective serotonin reuptake inhibitors are sometimes associated with increased cytotoxicity when combined with certain chemotherapy agents.⁶

“Another benefit of this antidepressant, and the reason it was selected as first line, is that it alleviates gastrointestinal symptoms (nausea) induced by chemotherapy and poor sleep related to distress and anxiety.”

Because of fatigue, depression, and anxiety, Mr Arnold notably lost interest in his routine activities. For the treatment of fatigue, he needed only conservative care such as physical therapy and energy conservation; no pharmacological intervention was required. During the course of depression treatment, it was important to focus on Mr Arnold's mood improvement based on depression symptoms that are psychologically based, rather than neurovegetative ones that are related to lung cancer such as fatigue, pain, dyspnea, weakness, insomnia, and poor concentration. Distinguishing physical symptoms due to cancer treatment is essential in this patient group.

The depression symptoms that were considered markers of depression response include feeling hopeless/helpless or unmotivated, easy crying, irritability, self-blaming, social isolation, and mood/affect change. The patient's quality of life and other meaningful elements of his life were also important to consider when following up on the treatment of depression and anxiety. Helping the patient's mood serves a dual purpose, both as a success in mental health treatment and a way to improve the patient's immune system and improve adherence to the lengthy cancer treatment program. Depression in cancer patients leads to higher rates of readmissions.⁷

Concluding Thoughts

When evaluating anxiety among patients with lung

cancer, it is also important to distinguish physiologically based dyspnea and anxiety from a psychological state.

Mr Arnold's anxiety could have started with a respiratory deficit, but it was later exacerbated by the fear of death, catastrophizing, as well as feeling hopeless and helpless. Besides the psychological trauma, going through 20 months of radiation and chemotherapy was an ordeal for Mr Arnold, as he struggled with poor quality of life due to severe pain induced by the treatment. Because pain is a multidimensional and complex experience, it was imperative to explore the psychospiritual dimension of his suffering during follow-up visits. Discussing his pain, fear, concern, loss of autonomy, and dignity helped relieve Mr Arnold's distress. Fortunately, he was not reluctant to talk about these concerns.

With a good response to the cancer treatment, Mr Arnold's grieving mostly resolved after successfully completing his treatment, with residual intermittent anxiety of disease recurrence.

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CLINICAL REFLECTIONS

A Brain-Based Approach to Psychotherapy

» Richard D. Lane, MD, PhD

Psychotherapy is one of the oldest items in the clinical toolkit. Yet, despite its familiarity, it remains somewhat mysterious. How does it actually work? What are the neural mechanisms by which psychotherapies (cognitive behavioral therapy [CBT], psychodynamic therapy, and others) create lasting changes in patients' mental health?

For several years, I have worked with other researchers in pursuing the answers to these questions into the frontiers of memory neuroscience. Our goal is to capitalize on major advances in our understanding of the neural basis of memory, emotion, and emotion-memory interactions. If we could start to explain the basic mechanism of action behind psychotherapy, then maybe we could understand how to conduct psychotherapy more effectively, with the ultimate goal of working with our patients to produce transformational and durable change.

The Frontiers of Memory Neuroscience

Recent studies have made important discoveries about the neural mechanisms underlying memory, and 4 are of particular interest (Table).¹⁻⁵

Drawing upon these observations, my colleagues and I hypothesized that there were 3 key ingredients to lasting change in psychotherapy:

1. activating problematic memories and the associated painful affect;
2. concurrently engaging new emotional experiences that change old memories through reconsolidation;
3. reinforcing the strength of new memories and their semantic structures by practicing new ways of behaving and experiencing the world in a variety of contexts.

We briefly discussed the application of this model to 4 different psychotherapy modalities including behavioral, cognitive behavioral (CBT), emotion focused (EFT), and psychodynamic psychotherapies in a previous article.⁴

Bringing the Research Into the Clinic

Realizing that there was much more to say about this new way of understanding change in psychotherapy, I coauthored a book that expands upon

our previous research in 3 sections.⁶ The basic science section includes chapters on emotion, memory, emotion-memory interactions, the role of language in shaping emotion and memory, and the role of sleep in memory consolidation and reconsolidation. The clinical section includes chapters from leading experts in psychodynamic psychotherapy, CBT, EFT, coherence therapy, and integrative approaches. Each author considers the role of memory reconsolidation in both psychotherapy and achieving lasting personal change. The final section includes chapters on recurrent maladaptive patterns, a computational neuroscience perspective on the proposed model, and a discussion of a proposed preclinical and clinical research agenda. Considerable effort was made within and

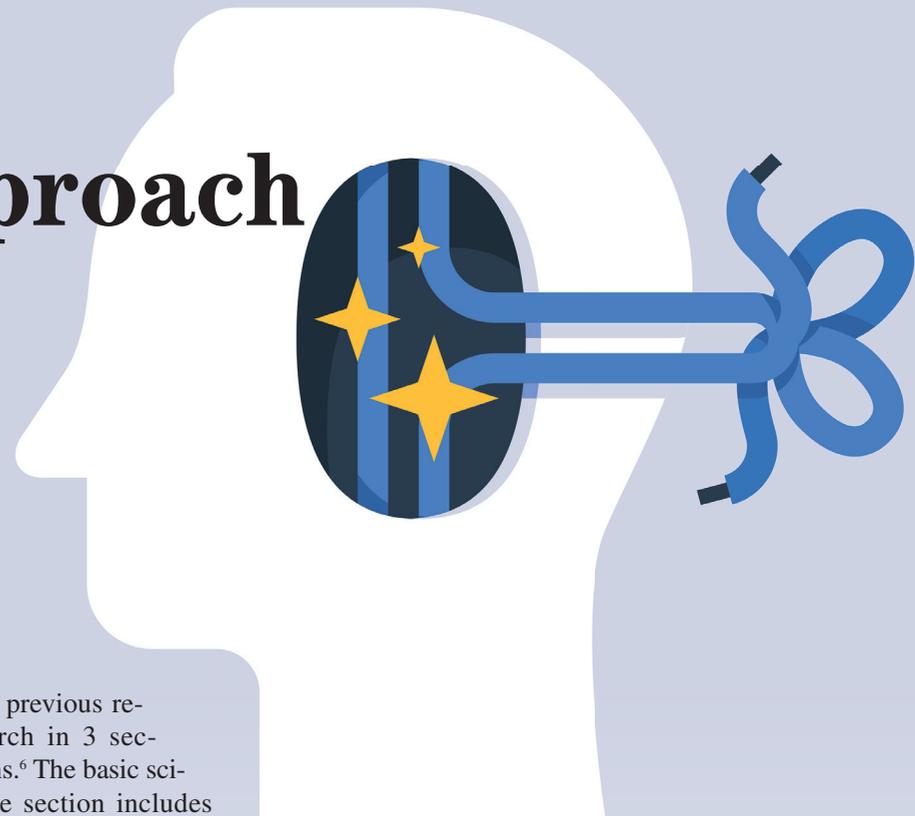
across chapters to promote cross-fertilization between basic science and clinical application.

If one takes this model seriously it could influence psychiatric practice in several ways. For example, it is useful to consider how interventions might be adjusted in therapies that have stalled or failed. Rather than talking about feelings with the goal of promoting insight, it is also important to experience feelings, especially the old painful feelings, from which individuals have protected themselves for years, and to juxtapose these feelings with corrective emotional experiences.

Another clinical implication emerges from the observation that consolidation of emotional memories occurs primarily during REM sleep. Because reconsolidation may work in the same way, medications that inhibit REM sleep may be counterproductive to enduring change in psychotherapy. It is, therefore, important to know that selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclics, and benzodiazepines inhibit REM sleep, whereas trazodone, bupropion, and mirtazapine do not.^{7,8} The book describes these and other implications, and provides a fresh perspective on how psychotherapy practice may be optimized and integrated in psychiatric care.

Table. Lessons From the Neuroscience of Memory¹⁻⁵

Neuroscientific Finding	Clinical Implication
1. Memories are not fixed entities.	Memories enter a labile state whenever they are reactivated, and they can be modified or updated with new information during a 4- to 6-hour window after reactivation.
2. Specific memories and general knowledge memory share neural mechanisms.	Specific episodic (event) memories and semantic (generalizable knowledge) memories are highly interrelated in that they share neural mechanisms, and the latter are a distillation of the former.
3. Memories that are emotionally charged are remembered better than those that are not.	Emotionally painful events can remain with patients for years, severely interfering with their mental wellbeing.
4. When memories are retrieved, their affiliated emotions can return too.	The activation of emotion appears to be a necessary ingredient of successful outcomes in psychotherapy. It allows the patient to reexamine past events and emotions, and build new, less painful emotional associations.



**Exploring the Backstory:
What Led to My Interest**

My interest in this topic emerged over the course of my 35-year career as an academic psychiatrist. I was initially trained as a clinical psychiatrist and psychodynamic psychotherapist and have continued to practice and supervise residents ever since. I was also fortunate enough to receive research training (resulting in a PhD in experimental psychology) that focused on cognitive neuroscience and functional neuroimaging of emotion. I have found the dialogue between the basic science of psychiatry and its clinical application to be particularly enriching and informative.

In my role as educator, I have become well acquainted with the challenges (eg, significant differences in the theoretical backgrounds, mindset, and clinical interventions re-

quired by these different approaches) psychiatry residents face in developing competence in CBT, psychodynamic psychotherapy, and supportive psychotherapy. Because there is a strong interest in finding common factors and common mechanisms across psychotherapy modalities, it occurred to me that a systems neuroscience perspective could provide an integrative mechanistic framework that would highlight commonalities instead of divergences. Moreover, the goal of integrating pharmacotherapy and psychotherapy is likely to be advanced by explaining how each works in brain-based terms.

Concluding Thoughts

It is important to emphasize that we have not yet established that change in psychotherapy occurs through memory reconsolidation. One of the

conclusions of our book is that a focus of intervention is recurrent maladaptive patterns, which can be understood as an expression of schemas. Schematic memory is a type of semantic memory and, as an area of neuroscientific investigation, it is relatively new. It remains to be demonstrated empirically that schematic memories can be updated with emotional information. If so, it must then be determined whether this applies to psychotherapy. Although research of this type is still underway, it might be argued that it is important to consider the clinical implications of this model if it were true.

Dr Lane is a professor of psychiatry, psychology, and neuroscience at the University of Arizona. Along with Lynn Nadel, PhD, Lane is the author of *Neuroscience of Enduring Change: Implications for Psychotherapy*.

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How Many Lives Have Been Saved by COVID-19 Vaccinations?

FROM THE PAGES OF
Medical Economics
SMARTER BUSINESS. BETTER PATIENT CARE.

» Keith A. Reynolds

According to a National Institutes of Health (NIH) study, COVID-19 vaccines have so far reduced the number of fatalities that would have occurred due to the disease by about 140,000. The study researchers examined data from between December 21, 2020, and May 9, 2021, to assess the impact of state-level vaccination campaigns. The investigators compared the amount of time each state took to reach a series of milestones, beginning with 5 doses per 100 adults and escalating to 120 doses per 100 adults. They also calculated the number of vaccine doses per 100 adults at the end of each week.

The researchers found that COVID-19 vaccines prevented more than 139,000 deaths during the first 5 months they were available. Although 570,000 Americans died due to COVID-19 through the study period, the researchers' model projected that there would have been 709,000 deaths without the vaccine.

In addition, the investigators estimated that the economic value of saving these lives was between \$625 billion and \$1.4 trillion.

The reduction in deaths varied across states. New York led, with vaccinations resulting in an estimated 11.7 fewer COVID-19 deaths per 10,000 people. Hawaii saw the smallest reduction, with 1.1 fewer deaths per 10,000.

"This study brings into focus the dramatic success of the early months of the nation's coronavirus vaccine rollout," reported Christopher Whaley, PhD, of the RAND corporation, who helped lead the research team, in an NIH news release.

"The researchers found that COVID-19 vaccines prevented more than 139,000 deaths during the first 5 months they were available."

The investigators noted, however, that the study had limitations, including an inability to distinguish between the role of vaccination and that of other factors—such as increases in natural immunity or social distancing policies—on the number of COVID-19 deaths.

These statistics are emerging as the nation gears up for another vaccination push: The federal government is considering third doses of the Pfizer and Moderna COVID-19 vaccines for Americans, to be taken about 8 months after their second dose.

Reportedly, this decision regarding a third dose came after Biden administration officials

reviewed a wide array of data and concluded that the additional shots are needed to maintain immunity against COVID-19. As this issue was going to press, the administration was not yet recommending an additional dose for those who received the Johnson & Johnson vaccine; data are still under review.

This move comes as the Delta variant has driven up the numbers of COVID-19 infections across the country and has led to a rash of breakthrough infections among individuals who are already vaccinated.

The US Food and Drug Administration (FDA) has already expanded the emergency use authorization for the Pfizer and Moderna 2-dose vaccines to allow for a third dose to the estimated 3% of Americans, or about 9 million people, who have weakened immune systems. The vaccines are believed to be less effective in this group of people, but the initial hope was that widespread vaccinations, leading to herd immunity, would protect the immunocompromised population. However, as of August 25, just slightly more than half of eligible Americans—167.1 million—have been fully vaccinated. □



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Reflections on Love, Work, Psychiatry, and Long Lives

» H. Steven Moffic, MD

“Love and work are the cornerstones of our humanness.”
— Sigmund Freud

Ezekiel Emanuel, MD, penned the controversial article “Why I Hope to Die at 75.”¹ Although he was not planning to end his life at the age of 75, he noted he was stopping any efforts to prolong his life, such as taking medications and undergoing other medical interventions. Not surprisingly, he was met with quick medical criticism.² Nevertheless, he reaffirmed his viewpoint 5 years later, in 2019.³

At the time he wrote the original article he was a mere 57; he was due to turn 64 on September 6, 2021. Perhaps becoming 64 fits his thesis, especially if you recall the lyrics of The Beatles’ song “When I’m Sixty-Four”:

*Will you still need me, will you still feed me
When I’m sixty-four?*

What was his ethical reasoning? Basically, he felt that only a small percentage of individuals continue to be active, engaged, and creative past 75 years old. He specified that play did not qualify, as it was not meaningful work. He did not seem to address the love part of Sigmund Freud’s statement; that is, one’s value to loved ones at the age of 75 and beyond.

This issue became personal to me—I turned 75 on May 5—when someone reminded me of Emanuel’s article. That, in turn, led me to recall that many of our psychiatrists’ eulogies over the years were given for those who died after the age of 75 and had continued to contribute to work, let alone love. Moreover, our newest eulogies seem to be relevant for that age consideration.

Below is a list of those eulogies, in order of their deaths, along with more than the usual focus on age. Unless referenced, as usual, sources are public obituaries and my personal knowledge.

Hagop Souren Akiskal, MD

Akiskal died on January 20, 2021.
He was 77 years old.

He was an internationally recognized expert not only on bipolar disorder but also on a new area of psychiatric attention— affective temperaments. As a by-product of his focus on bipolar disorder, he noted

that lithium markedly reduced suicide risk. Besides being a prolific author, writing more than 500 articles and 25 books, he was a persuasive speaker and presenter, often referring to ancient masters of the subject. He was likened to a brilliant jazz soloist who played the same piece differently each time.

It is rare to find memorial testimonies of any psychiatrist in as many psychiatric publications as Akiskal has received, including from the World Psychiatric Association; *Annals of General Psychiatry*; and the American Psychiatric Association (APA) *Psychiatric News*.^{4,6} A paper in memory of him was coauthored by 10 colleagues from 8 countries, a global village of psychiatrists.⁷ Akiskal, himself, spoke 6 languages.

Joseph Napoli, MD

Napoli died on April 9, 2021,
just short of the age 75.

Before his terminal illness was apparent, he had become Speaker of the Assembly of the APA.

His area of expertise was posttraumatic stress disorder, and he received the 2003 APA Bruno Lima Award for the care and understanding of victims of disasters. He coauthored the book *Resiliency in the Face of Disaster and Terrorism: 10 Things to Do to Survive*.

Near the end of his life, when I interacted with him the most, he became an activist for addressing climate concerns. He passed information on climate change skeptics to his colleagues for as long as possible.

Charles E. (“Charlie”) Riordan, MD

Riordan died on July 17, 2021, at the age of 83.

After developing maintenance treatment for opiate addiction, Riordan became a longtime faculty member at Yale School of Medicine, establishing a pioneering substance abuse remedy. He was felt to be the medical glue of the system. Riordan was a stickler for perfection, but he could also defuse tension with cherished jokes. As an offshoot of his substance abuse expertise, he consulted for Major League Baseball.

He retired from Yale in 2007 but continued in some private practice and helped at the Connecticut Hospice. However, his major focus in his later years was as Pop to his 11 grandchildren. On family trips, he often would get up early to buy a big bag of doughnuts for his grandchildren, with the unspoken goal of spending time talking with them.

Robert Paul Liberman, MD

Liberman died on August 20, 2021.
He was 84 years old.

In 2017, he offered to give community psychiatrists copies of his magnum opus, *Recovery From Disability: Manual of Psychiatric Rehabilitation*. Of course, many accepted his offer. I did, too, even though I already had an autographed copy. Not much later, he announced his retirement from his full-time position at the University of California, Los Angeles (UCLA). And, as usual, he continued to offer me support and advice, as in this communication:

“When we get to the age of 78, we see the important things more clearly—including time with family and the beauty around us... Your comments on the AACP [American Association of Colleges of Pharmacy] round-robin are always ‘right on’! Keep on and on and on!!”

Liberman was one of the world’s experts on psychiatric rehabilitation. More broadly, he kept alive a decreasing therapeutic focus in psychiatry, that of behaviorally oriented treatment. In fact, that was the focus of his first book, *A Guide to Behavioral Analysis and Therapy*, which was published in 1972. Unfortunately, he recognized—and lamented—that reimbursement never caught up to the complexity and time necessary to fulfill his expert guidelines.

Less well-known is that he was also an activist regarding the Vietnam War. And, when he deemed it appropriate, he self-disclosed about his own affective disorder. Perhaps he was most proud of his family as well as spending time exploring other countries and cultures with them.

Collegial recognition poured in quickly after his death was made public. My favorite came from a colleague who referred to Liberman, his former boss and mentor, as “our Jewish godfather”: If not for Liberman and the center he established at UCLA, this man would not have met his wife, and his family would not exist.

When We Are 75

Perhaps Emanuel was not too familiar with the work and lives of psychiatrists, and he does not appear to have consulted with any while writing his manifesto. Not limited by the need for physical dexterity, as long as their cognitive ability continues, psychiatrists traditionally work to late in life, often to death—at least until burnout became a more common limitation. As this group of eulogies conveys, once again, psychiatrists can work well up to age 75 and beyond. Besides that, they often have cultural and family interests that make their lives so valuable to others. Emanuel may change his mind when the reality of being 75 becomes imminent.

Regardless, let us recall and celebrate these well-lived psychiatrist lives, close to 75 and beyond.

Dr Moffic is an award-winning psychiatrist who has specialized in the cultural and ethical aspects of psychiatry. A prolific writer and speaker, he received

the one-time designation of Hero of Public Psychiatry from the Assembly of the American Psychiatric Association in 2002. He is an advocate for mental health issues related to climate instability, burnout, Islamophobia, and anti-Semitism. He serves on the Editorial Board of Psychiatric Times™.

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Divining the Truth: Anti-Vaxxers, Water Witches, and the Limits of Reason

“Come now, and let us reason together.”—Isaiah 1:18

“Reason is, and ought only to be, the slave of the passions.”

—David Hume¹

» Ronald W. Pies, MD

After being fully vaccinated against COVID-19, I ventured out for a long-postponed haircut without wearing a mask. The pleasant but tempestuous woman who regularly cuts my hair had received the single-shot Johnson & Johnson vaccine, but when I told her I had received 2 doses of the Pfizer vaccine, she looked horrified. “Oh, no!” she said, “That vaccine is going to rewrite your DNA and leave your immune system damaged for life!” With her scissors 3 inches from my face, I decided this was not the time to challenge her or to explain that, no, the mRNA vaccines do not rewrite one’s genetic code or destroy the immune system.

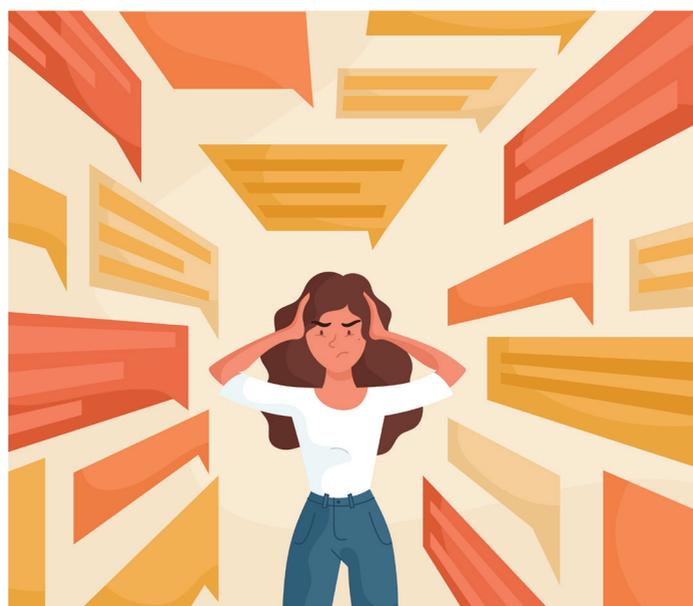
Then, a few days ago, I read about the increasing use of so-called water witches in California, which is experiencing extreme drought conditions. According to *The New York Times*, these “water dowsers” claim that they can “... locate streams of water in the fractures in the earth’s bedrock, using 2 L-shaped rods that together resemble an old-fashioned television antenna.”² These individuals are now heavily booked and well paid for their services, despite the fact that hydrogeologists describe water dowsing as “totally without scientific merit.”²

The common thread in these personal vignettes is, of course, a deep-seated denial of science and a mistrust of scientific *experts*—a word that is nowadays pronounced with a kind of dismissive hiss. Indeed, experts in epidemiology and infectious disease, such as Anthony Fauci, MD, are not merely doubted by a substantial proportion of the public—they are threatened with bodily harm for advocating vaccination against COVID-19.³

It is easy to explain away such science denial as the result of mistaken information and biased reasoning, exacerbated by grossly misleading claims on social media.⁴ To be sure, these factors do contribute to science denial and the derogation of scientific authority. As physicians, we have an obligation to provide our patients with accurate

information that might counteract such irrational and unfounded beliefs.⁵

But as psychiatrists, we know that reason has its limitations, absent a deep understanding of the feelings—indeed, the *passions*—that shape human belief and behavior. The great Scottish philosopher David Hume (1711-1776) understood this well, arguing, in his *Treatise of Human Nature*, that “... reason is, and ought only to be, the slave of the passions.”¹ Accord-



ing to philosopher AT Nuyen, Hume was not negating the importance of reason in shaping human belief and behavior, but merely putting it in proper perspective—arguing, in effect, that “... reason alone does not move one to act. The force that propels one to action is the passion, whether it be love, or anger, or pride, or envy, or fear, or desire.”¹

Hume’s great insight has been amply confirmed by modern-day psychological research, notably that of Robert Sapolsky, PhD, a professor of neurology and neurosurgery at Stanford University.⁶ Sapolsky’s studies of cognitive function have convinced him that, “You can’t reason somebody out of something they weren’t reasoned into in the first place,” and that “We’re certainly set up to only have resonating in our head the stuff we want to hear.” He adds that, “... people who are least curious, most

unwilling to explore novelty, [and] most reflexively hostile about it are people who are anxious.”⁶

And who better to empathize with and explore anxiety than psychiatrists? Indeed, Sapolsky urges us to emulate the teenager, whose “... deeply felt sense of empathy” is often lacking in adults. Had I been doing therapy with someone like the woman who cuts my hair, I would have homed in on the anxiety that probably underlay her unfounded beliefs about COVID vaccines. If I were working therapeutically with the rancher or vineyard owner shelling out good money to a “water witch,” I might focus on the understandable feelings of despair and desperation driving that behavior. Yes, I

would also gently guide these individuals to sources of accurate information—but only after connecting with them on an *emotive* level. As another philosopher—Blaise Pascal (1623-1662)—wisely put it, “The heart has its reasons which reason knows nothing of ... We know the truth not only by the reason, but by the heart.”⁷

Dr Pies is professor emeritus of psychiatry and lecturer on bioethics and humanities, SUNY Upstate Medical University; clinical professor of psychiatry, Tufts University School of Medicine; and editor in chief emeritus of Psychiatric Times™ (2007-2010). He is the author, most recently, of *The Levitov Trilogy* and *Just Take it One Miserable Day at a Time*.

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- acute narrow-angle glaucoma

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- Use alone and with other CNS depressants may lead to potentially fatal respiratory depression. Alcohol should be avoided, and other CNS depressants used with caution.

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

Risk of Paradoxical Reactions

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

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

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

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DOSAGE AND ADMINISTRATION

Recommended Dosage

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

Administration Information

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

Dosage Increase for Inadequate Clinical Response

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

Discontinuation or Dosage Reduction

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

Concomitant Use with UDP-glucuronosyltransferase (UGT) Inhibitors

If a UGT inhibitor is initiated during treatment with LOREEV XR, discontinue LOREEV XR and switch to lorazepam tablets to reduce the dosage.

CONTRAINDICATIONS

LOREEV XR is contraindicated in patients with:

- hypersensitivity to benzodiazepines or to any of the ingredients in LOREEV XR
- acute narrow-angle glaucoma

WARNINGS AND PRECAUTIONS

Dependence and Withdrawal Reactions

Acute Withdrawal Reactions

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

Protracted Withdrawal Syndrome

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

Central Nervous System (CNS) Depression

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

Patients With Depression or Psychosis

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

Risk of Paradoxical Reactions

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

Allergic Reactions to FD&C Yellow No. 5

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

Neonatal Sedation and Withdrawal Syndrome

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

Risk in Patients With Impaired Respiratory Function

In patients with impaired respiratory function, respiratory depression and apnea have been reported with benzodiazepines. Closely monitor patients with impaired respiratory function. If signs and symptoms of respiratory depression or apnea occur, consider discontinuing LOREEV XR.

Laboratory Tests

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

ADVERSE REACTIONS

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

Blood and Lymphatic System Disorders: agranulocytosis, leukopenia, pancytopenia, thrombocytopenia;

Endocrine Disorders: SIADH;

Eye Disorder: eye function/visual disturbance (including diplopia and blurred vision);

Gastrointestinal Disorder: constipation and gastrointestinal symptoms, including nausea;

General Disorders and Administration Site Conditions: asthenia, fatigue, hypothermia;

Hepatobiliary Disorders: jaundice;

(Cont'd)

(Cont'd)

Immune System Disorders: anaphylactoid reactions, hypersensitivity reactions;

Investigations: increase in bilirubin, increase in liver transaminases (including elevated LDH), increase in alkaline phosphatase;

Metabolism and Nutrition Disorders: change in appetite, hyponatremia;

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

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

Reproductive System and Breast Disorders: impotence;

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

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

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

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

Lactation

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

Pediatric Use

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

Geriatric Use

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

Hepatic Impairment

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

DRUG ABUSE AND DEPENDENCE

Controlled Substance

LOREEV XR contains lorazepam, a Schedule IV controlled substance.

Abuse

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

Dependence

Physical Dependence

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

Acute Withdrawal Signs and Symptoms

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

Protracted Withdrawal Syndrome

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

Tolerance

Tolerance to LOREEV XR may develop from continued therapy.

OVERDOSAGE

Clinical Experience

In postmarketing experience, overdose with lorazepam has occurred predominantly in combination with alcohol and/or other drugs.

Manifestations of overdose include varying degrees of CNS depression, ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion, paradoxical reactions, dysarthria, and lethargy. In more serious cases, symptoms may include ataxia, hypotonia, hypotension, cardiovascular depression, respiratory depression, hypnotic state, coma, and death.

In case of an overdosage, consult a Certified Poison Control Center at 1-800-222-1222 for latest recommendations.

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LOR-PR-004

SECTION EDITOR JAMES A. BOURGEOIS, MD

Exploring Vital Amines: The Who, What, When, Where, Why, and How of B₁₂ Deficiency

This article is the second of a 3-part series that aims to highlight and review the prevalence, risk factors, clinical manifestations, diagnostic recommendations, proposed mechanisms of disease, and current treatment recommendations of folate, B₁₂, and thiamine deficiencies. The first article ran in the March 2021 issue.

» Dustin DeMoss, DO; Olla Elbasheer, MD; and Nayana Kunnel, DO; Mahi Raju

Exploring Vitamins

As reviewed in the previous article, key nutrients—or what Casimir Funk, PhD, termed *vital amines*—are essential to maintaining good health. Deficiencies in these key nutrients lead to certain pathognomonic disease states, as Funk initially observed when he fed birds a diet of only polished rice and they developed a diffuse polyneuritis (beriberi). Afterwards, the same birds were fed a diet of brown rice, and their “nervous symptoms rapidly disappeared.”¹ What did this experiment establish? The importance of vital amines, or as we know them, *vitamins*.

Vitamins can be broadly delineated into 2 categories: water-soluble and fat-soluble. Water-soluble vitamins are absorbed rapidly via the gastrointestinal tract and distributed widely in various body tissues; however, as these vitamins are water-soluble, they are not efficiently stored in tissues. Therefore, these vitamins require regular consumption (either through diet or supplementation) to avoid deficiency states. Fat-soluble vitamins, on the other hand, are more easily stored, typically in adipose tissue, and require less frequent intake.² Examples of water-soluble and fat-soluble vitamins can be found in **Table 1**.²

What is Vitamin B₁₂?

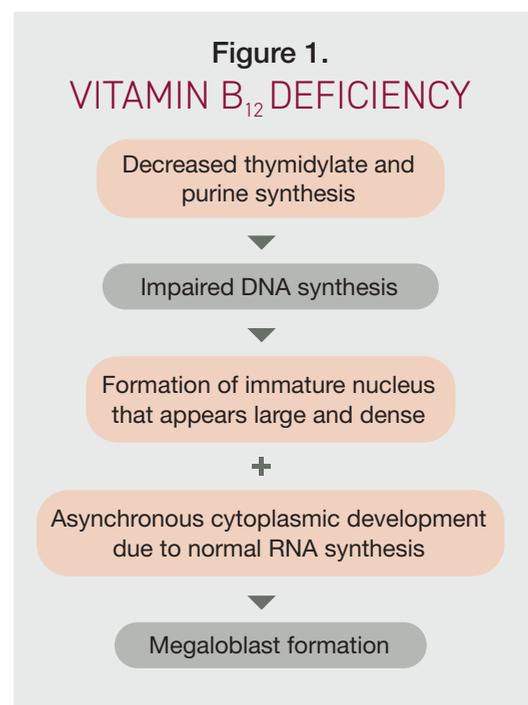
B₁₂ (cobalamin) is a water-sol-

uble vitamin that is found in certain foods and is required for DNA synthesis and the formation of several hematologic elements, such as red blood cells (RBCs), white blood cells, and platelets.³ Individuals who have low levels of vitamin B₁₂, due to either increased demand or poor absorption, are labeled vitamin B₁₂ deficient. Vitamin B₁₂ deficiency can lead to the formation of abnormal hematopoietic precursor cells such as megaloblastic RBCs, as seen in **Figure 1**.

Vitamin B₁₂ deficiency is not only problematic for hematopoiesis; it also has severe neuropsychiatric consequences, including cognitive impairment, depression, insomnia, psychosis, peripheral sensory deficits, and weakness. Lhermitte sign (**Figure 2**)⁴ can be tested by flexing the neck and assessing for shock-like sensations radiating to the feet. The mechanism is better understood for neuropathies (primarily dorsolateral myelopathy) associated with this deficiency as opposed to neuropsychiatric conditions. Most theories suggest that elevated methylmalonic acid (MMA) levels found in vitamin B₁₂ deficiency may lead to demyelination of the peripheral nervous system and central nervous system.⁵ MMA accumulates in cells due to lack of vitamin B₁₂ as a cofactor in the conversion of MMA to succinyl Co-A in cell metabolism.

Why Does B₁₂ Deficiency Happen?

There are several potential causes of vitamin B₁₂ defi-



ciency. Autoimmune pernicious anemia is the most common cause of vitamin B₁₂ deficiency. Intrinsic factor (IF) and gastric parietal cells are attacked by gastric autoantibodies. IF is a glycoprotein that binds cobalamin and aids in the absorption of vitamin B₁₂ in the terminal ileum. The depletion or lack of IF in pernicious anemia causes cobalamin deficiency.⁶ Other causes such as poor absorption related to pancreatic insufficiency, gastrectomy, intestinal surgeries, and inflammatory bowel disorders can also contribute to poor vitamin B₁₂ absorption. Intestinal infections competing for vitamin B₁₂ absorption such as small intestinal bacterial overgrowth or a parasitic infection should also be considered. Genetic disorders affecting absorption and transport of vitamin B₁₂, such as transcobalamin deficiency, are currently being studied. Several medications can also lead to vitamin B₁₂ deficiency via impaired absorption, metabolism, and utilization; these are listed in **Table 2**.^{7,8} Pure nutritional deficiency is usually only seen in strict vegans and is extremely rare.⁹ Selected food sources of vitamin B₁₂ can be found in **Table 3**.⁹

Table 1. Water-Soluble vs Fat-Soluble Vitamins²

Water-soluble
B ₁ (Thiamine)
B ₂ (Riboflavin)
B ₃ (Niacin)
B ₅ (Pantothenic acid)
B ₆ (Pyridoxine)
B ₇ (Biotin)
B ₉ (Folate)
B ₁₂ (Cobalamin)
Vitamin C (Ascorbic acid)
Fat-soluble
Vitamin A (Retinol)
Vitamin D (Ergocalciferol)
Vitamin E (Tocopherol)
Vitamin K (Phytonadione)

Figure 2. Lhermitte's Sign⁴

Who Is at Highest Risk for This Disorder?

Some people are at more of an increased risk of vitamin B₁₂ deficiency than others. Older adults are at increased risk of vitamin B₁₂ deficiency due to gastric malabsorption secondary to gastric atrophy, chronic *H. pylori* infection, increased probability of gastric surgery history, and chronic use of medications like metformin and proton pump inhibitors.¹⁰ In patients with alcoholic liver disease, cobalamin levels may remain falsely elevated or normal despite low concentrations of liver tissue cobalamin and its active metabolites. This leads to a functional cobalamin deficiency. Proposed mechanisms of action include impaired uptake of serum cobalamin by the damaged liver, impaired storage of cobalamin in the liver that causes it to leak out, and reduced hepatic ability to synthesize transcobalamin. Vitamin B₁₂ treatment has proven beneficial to some alcohol-dependent patients with megaloblastic anemia.¹¹ Older adults, individuals taking the medications listed in **Table 2**,^{7,8} those with alcohol use disorders, pure vegans, and individuals with poor access to adequate nutrition (either through economic limitations or malabsorptive limitations) are at highest risk.

In 2008, the World Health Organization recommended vitamin B₁₂ fortification standards in order to prevent deficiency in high-risk populations. Since then, some nations have implemented these strategies and are working to improve dosing standards. The United States has yet to implement mandatory vitamin B₁₂ fortification, but certain foods, such as cereals, can be found to be fortified voluntarily.

When Should Screening and Prevention Be Done?

Screening and testing should occur in the following groups: those at high risk; individuals who

have evidence of a macrocytosis or hyper-segmented neutrophils on peripheral blood smear; those with unexplained neurological conditions (eg, cognitive decline, weakness, ataxia, paresthesia); and those with unexplained psychosis and mood disturbances. Serum cobalamin levels are not always reliable in detecting vitamin B₁₂ deficiency. If an asymptomatic high-risk patient presents with low to normal serum vitamin B₁₂ levels, obtain serum homocysteine and MMA levels as a confirmatory test.¹² If pernicious anemia is suspected, confirm the diagnosis by obtaining anti-IF antibody levels and serum gastrin/pepsinogen levels.¹²

Those aged 50 years or older and strict vegetarians may benefit from vitamin B₁₂ supplements or food fortified with vitamin B₁₂, as the crystalline formulation is better absorbed than natural dietary cobalamin. Following gastric bypass surgery, patients should supplement with vitamin B₁₂, 1 mg daily.¹³

Where Is This Condition Most Prevalent?

In the United States, older adults have the highest prevalence of vitamin B₁₂ deficiency. In the United States and the United Kingdom, the prevalence of vitamin B₁₂ deficiency was found to be 6% in adults 60 years of age or younger. In adults 60 years of age or older, the prevalence increases to 20%.¹⁴

How Do You Diagnose and Treat B₁₂ Deficiency?

Patients exhibiting macrocytic anemia on initial complete blood count and peripheral blood smear should be evaluated for both folate and vitamin B₁₂ deficiency, as these 2 conditions often present simultaneously. This can be done by assessing serum folate and B₁₂ levels. The diagnosis of vitamin B₁₂ deficiency is usually made when serum levels are less than 111 pmol/L (150 pg/mL).¹⁵ Measurement of serum homocysteine and MMA can also aid in differentiating between folate and vitamin B₁₂ deficiencies. In vitamin B₁₂ deficiency, both homocysteine and MMA levels can be elevated.

Repletion with vitamin B₁₂ is the standard treatment. The cause of the deficiency will dictate how one administers the medication and how much to dose. Those with poor absorption, altered anatomy, and/or neurological/neuropsychiatric manifestations would likely benefit more from parenteral than from oral administration. Typical dosing for adults is 1000 mcg parenterally several times per week until the deficiency is corrected, then once per month.¹⁶ High-dose oral vitamin B₁₂ and intramuscular vitamin B₁₂ are both effective treatments for vitamin B₁₂ deficiency.¹²

Concluding Thoughts

Vitamin B₁₂ is a key nutrient that is essential for our hematologic and neuropsychiatric functioning. With the prevalence of vitamin B₁₂ deficiency reaching

Table 2. Medications That Cause Vitamin B₁₂ Deficiency^{7,8}

Drug class	Mechanism that induces vitamin B ₁₂ deficiency
H2 receptor antagonist ■ ranitidine & famotidine	Decreases secretion of IF and thus impairs absorption
Proton pump inhibitors ■ omeprazole, lansoprazole	Decreases secretion of gastric acid and thus impair dietary B ₁₂ absorption.
Biguanides ■ metformin	Decreases IF secretion and disrupts B ₁₂ /IF uptake at the ileal membrane
Clofibrate and other fibrates	Can impair absorption
Nitrous oxide	Inactivates vitamin B ₁₂ , thus inhibiting methionine synthase activity.
Aminoglycosides	Decreases absorption & biosynthesis, increases elimination, interferes with metabolism.
Chloramphenicol	Reduces absorption, opposes erythropoietic activity
Anticonvulsants (eg, phenytoin, phenobarbital, primidone)	Reduces absorption
Colchicine	May interfere with absorption and interferes with metabolism by reducing IF/B ₁₂ receptors.
Methotrexate	Interferes with folate metabolism & increases risk of vitamin B ₁₂ deficiency.
Oral contraceptives	Decreases vitamin B ₁₂ levels
Reverse-transcriptase inhibitor Antiretroviral agents ■ zidovudine	B ₁₂ malabsorption
Extended release potassium preparation	Reduces absorption
Aminosalicylic acid	Reduces absorption

IF, intrinsic factor.

Table 3. Selected Food Sources of Vitamin B₁₂⁹

Food	Daily value
Meats	
Beef liver, braised, 3 ounces	1178%
Cheeseburger, double patty, and bun, 1 sandwich	35%
Beef, top sirloin, broiled, 3 ounces	23%
Beef taco, 1 soft taco	15%
Ham, cured, roasted, 3 ounces	10%
Chicken, breast meat, roasted, 3 ounces	5%
Fish	
Clams, cooked, 3 ounces	1402%
Salmon, sockeye, cooked, 3 ounces	80%
Trout, rainbow, farmed, cooked, 3 ounces	58%
Tuna fish, light, canned in water, 3 ounces	42%
Dairy	
Milk, 1% fat, 1 cup	18%
Yogurt, fruit, low-fat, 8 ounces	18%
Cheese, Swiss, 1 ounce	15%
Grains	
Breakfast cereals, fortified with 100% of the DV for vitamin B ₁₂ , 1 serving	100%
Breakfast cereals, fortified with 25% of the DV for vitamin B ₁₂ , 1 serving	25%

DV, daily value.

20% in certain populations, it is crucial to recognize patients who are at risk and/or require treatment. Vitamin B₁₂ replacement is relatively inexpensive and can be lifesaving when administered via the appropriate route and at the appropriate dosage.

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Prompts (for Doctors Who Write Poetry)

Richard Berlin, MD

—After Dante Di Stefano

No one is a poet from eight to twelve and from two to six. Whoever is a poet is one always, and is continually assaulted by poetry. —Jorge Luis Borges

Write yourself scared the first day
of med school, dying to cure the world.
Write the anatomy lab's cold steel table,
your cadaver's swollen face, formalin's
funk soaked into your skin, the scalpel's
fierce friction when you severed her breast.
Write your first patient, Vinny T,
a tremulous, belly-bloated alcoholic
veteran, puking blood, cursing
your incompetence and fear.
Write what happened to your heart
when he recovered, corralled your shoulder,
and announced to a twenty bed ward,
This is the doctor who cured me!
Write the names of hospitals you'll never forget—
Cook County, Cabrini, Rainbow Babies,
the Reed Zone Center, where Jesus Christ himself
blessed you as his psychiatrist and disciple,
the miracle when his face appeared above
the purple-robed Dean as you swore your oath.
Write elegies for prescription pads and progress
notes you carved with ballpoint pens,
odes to the stethoscope and Queen's Square hammer,
sonnets for nurses who taught you
to care for patients with a caregiver's love.
Write mentors who modeled bedside manners,
the way their gaze steadied spinal needles
you threaded home. Write about not having time
to write, hours you read journals, double-checked doses,
worried who might crash. Write the fear of getting sued.
Write the cemetery where you commune with dead patients.
Praise their lessons. Then write yourself perfect,
your *Hallelujah!* when you nailed a diagnosis
and felt like a god. Write a limerick about doctors
who feel like gods. Write every day. Write
what you love. Write a career adding up to a life.



Dr Berlin has been writing a poem about his experience of being a doctor every month for the past 23 years in *Psychiatric Times*™ in a column called "Poetry of the Times." He is instructor in psychiatry, University of Massachusetts Medical School, Worcester, MA. □

BIPOLAR UPDATE

Bipolar Depression

How Not to Miss the Diagnosis

» David N. Osser, MD

Although the *DSM-5* diagnostic criteria for a major depressive episode are the same for unipolar and bipolar disorders, these episodes differ in their natural past history (ie, patients with bipolar disorders will have discrete episodes of hypomanias or manias), age of onset, suicide risk, associated comorbidities, and biological correlates. And, most importantly, they differ dramatically in the medications that are effective. Thus, it is critical to diagnose them correctly.

To do so, you must take a good history for hypomania or mania, because this is where diagnostic error commonly occurs. Start by informing the patient how important it is to have the correct diagnosis for effective treatment and that being wrong about the diagnosis can lead to the wrong treatment—which is at best ineffective and at worst very harmful (eg, antidepressants can cause a malignant transformation in bipolar disorder to a rapid cycling and treatment-resistant condition).¹⁻³ This warning to the patient hopefully overrides their potential reluctance to disclose manic symptoms because of the stigma of the diagnosis, their enjoyment of the experience, or their belief that it represents their normal mood and energy that they would like to return to and maintain.

Painting a Picture of Mania

Start by describing an episode of mania or hypomania. Patients often wake up feeling, for no particular reason, unusually energetic, with thoughts racing about millions of things they want to get done. They want to start new projects, clean and organize the house, add to their possessions, contact neglected friends. They set out to do those projects and then they go-go-go day and night, feeling a lessened need for sleep or maybe skipping sleep completely for a night or so. They almost invariably spend money to fund the ventures or add to hobbies, clothes, or possessions. Often, they already have plenty of what they are buying and they later recognize that the purchases were unnecessary. They discount the importance of other bills, thinking they will figure out how to pay those at some future date, believing the new purchases to be more important.

Explain that during mania their speech is accelerated and increased in quantity and volume. This tends to be noticed by others, who will advise

Table. Factors That May Signal the Need to Change Diagnosis From Unipolar MDD to BD

Family history of bipolar disorder

A younger age of onset

Panic and/or anxiety

A family history of completed suicide

Past poor response to antidepressants (even 1 failed adequate trial of an antidepressant is reason to pause and wonder whether the diagnosis of bipolar disorder was missed; do not wait until there have been 5 to 10 failed trials)

A history of treatment-emergent irritability, agitation, or suicidality with antidepressants

Psychotic features

Postpartum depression or psychosis

BD, bipolar disorder; MDD, major depressive disorder.



them to “slow down” so they can be understood. Friends and family may see their plans as impractical, unrealistic, or risky, but patients in the grip of mania will ignore this feedback and often lash out and become irritable and defensive. At work, if there are disagreements with the boss, there can be loud arguments, and the person with mania can impulsively quit or get fired, which they later regret.

Their disinhibited speech can also include embarrassing self-disclosures, undiplomatic criticisms of others, or inappropriate sexualized content. Their property can be littered with tools and supplies for projects that were never finished, because when the manic episode ends, they lose all interest in the activity. Parts of their house may be partly demolished in preparation for the project and then stay that way for years, because when the

next manic episode begins, they usually start an entirely different project. Make it clear to the patient that the episodes you are talking about last at least a few days and nights, often more.

At this point, stop and see if the patient recognizes these behavioral patterns. If it is unclear, bring up some additional symptoms: social overactivity, hazardous driving patterns, uncharacteristically starting conversations with strangers, and commonly sexual preoccupations and overactivity (this is a cause, although not the only one, of infidelity in established relationships, often resulting in the end of the primary relationship). It is often best to leave inquiries about sexual indiscretions to a later time due to possible embarrassment for them, but by the time you bring it up, you might get a very emphatic response of “absolutely!” about this symptom.

Diagnosis and Treatment

If the patient reports that these events do occur, get details about how long they last, how frequently the behaviors occur, and whether they cause significant impairment in social or work relationships, have legal consequences, or result in financial hardship. This will determine whether the patient meets the criteria for bipolar I or II, and rapid versus nonrapid cycling.

If the patient does not report criteria-meeting manic episodes, it is possible that they have prebipolar depression and could have a hypomanic or manic episode in the future.⁴ Initial manias have occurred in elderly patients after decades of depressions. A number of factors may predict when a unipolar major depressive disorder diagnosis could change to a bipolar disorder (**Table**).⁴ If enough predictors are present, including failure on previous antidepressant trials, consider treating the depression as a bipolar depression and taper off any antidepressants as you do so.

Dr Osser is associate professor of psychiatry at Harvard Medical School and co-director, US Department of Veterans Affairs National Bipolar Disorders Telehealth Program. The author reports no conflicts of interest concerning the subject matter of this article.

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CAPLYTA FOR SCHIZOPHRENIA IN ADULTS

THIS ISN'T JUST A COFFEE RUN.

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.



IT'S REAL
PROGRESS.

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

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

- **Orthostatic Hypotension and Syncope.** Monitor heart rate and blood pressure and warn patients with known cardiovascular or cerebrovascular disease. Orthostatic vital signs should be monitored in patients who are vulnerable to hypotension.
- **Falls.** CAPLYTA may cause somnolence, postural hypotension, and motor and/or sensory instability, which may lead to falls and, consequently, fractures and other injuries. Assess patients for risk when using CAPLYTA.
- **Seizures.** Use CAPLYTA cautiously in patients with a history of seizures or with conditions that lower seizure threshold.
- **Potential for Cognitive and Motor Impairment.** Advise patients to use caution when operating machinery or motor vehicles until they know how CAPLYTA affects them.
- **Body Temperature Dysregulation.** Use CAPLYTA with caution in patients who may experience conditions that may increase core body temperature such as strenuous exercise, extreme heat, dehydration, or concomitant anticholinergics.
- **Dysphagia.** Use CAPLYTA with caution in patients at risk for aspiration.

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

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

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

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

Reference: 1. CAPLYTA prescribing information, 2019.

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CAPLYTA[®]
(lumateperone) capsules
42 mg

Brief Summary of Full Prescribing Information.

CAPLYTA™ (lumateperone) capsules, for oral use
Initial U.S. Approval: 2019

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

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. Reactions have included pruritus, rash (e.g. allergic dermatitis, papular rash, and generalized rash), and urticaria.

WARNINGS AND PRECAUTIONS

Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in placebo-treated patients. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. CAPLYTA is not approved for the treatment of patients with dementia-related psychosis.

Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis: In placebo-controlled trials in elderly subjects with dementia, patients randomized to risperidone, aripiprazole, and olanzapine had a higher incidence of stroke and transient ischemic attack, including fatal stroke. CAPLYTA is not approved for the treatment of patients with dementia-related psychosis.

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

Tardive Dyskinesia: Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with antipsychotic drugs. The risk appears to be highest among the elderly, especially elderly women, but it is not possible to predict which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. The risk of tardive dyskinesia and the likelihood that it will become irreversible increase with the duration of treatment and the cumulative dose. The syndrome can develop after a relatively brief treatment period, even at low doses. It may also occur after discontinuation of treatment. Tardive dyskinesia may remit, partially or completely, if antipsychotic treatment is discontinued. Antipsychotic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome, possibly masking the underlying process. The effect that symptomatic suppression has upon the long-term course of tardive dyskinesia is unknown. Given these considerations, CAPLYTA should be prescribed in a manner most likely to reduce the risk of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients: 1) who suffer from a chronic illness that is known to respond to antipsychotic drugs; and 2) for whom alternative, effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, use the lowest dose and the shortest duration of treatment producing a satisfactory clinical response. Periodically reassess the need for continued treatment. If signs and symptoms of tardive dyskinesia appear in a patient on CAPLYTA, drug discontinuation should be considered. However, some patients may require treatment with CAPLYTA despite the presence of the syndrome.

Metabolic Changes: Antipsychotic drugs have caused metabolic changes, including hyperglycemia, diabetes mellitus, dyslipidemia, and weight gain. Although all of the drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile. **Hyperglycemia and Diabetes Mellitus -** Hyperglycemia, in some cases extreme and associated with ketoacidosis, hyperosmolar coma or death, has been reported in patients treated with antipsychotics. There have been reports of hyperglycemia in patients treated with CAPLYTA. Assess fasting plasma glucose before or soon after initiation of antipsychotic medication and monitor periodically during long-term treatment. In pooled data from short-term (4- to 6-week), placebo-controlled trials of adult patients with schizophrenia, mean changes from baseline and the proportion of patients with shifts from normal to greater than normal levels of fasting glucose in patients treated with CAPLYTA were similar to those in patients treated with placebo. In an uncontrolled open-label trial of CAPLYTA for up to 1 year in patients with stable schizophrenia, the percentages of patients with shifts in fasting glucose and insulin values from normal to high were 8% and 12%, respectively. 4.7% of patients with normal hemoglobin A1c (<6.5%) at baseline developed elevated levels (≥6.5%) post-baseline. **Dyslipidemia -** Antipsychotics have caused adverse alterations in lipids. Before or soon after initiation of antipsychotic medications, obtain a fasting lipid profile at baseline and monitor periodically during treatment. In pooled data from short-term (4- to 6-week), placebo-controlled trials of adult patients with schizophrenia, mean changes from baseline and the proportion of patients with shifts to higher levels of fasting total cholesterol and triglycerides were similar in patients treated with CAPLYTA and placebo. In an uncontrolled open-label trial of CAPLYTA for up to 1 year in patients with stable schizophrenia, the percentages of patients with a shift from normal to high were 8%, 5%, and 4% for total cholesterol, triglycerides, and LDL cholesterol, respectively. **Weight Gain -** Weight gain has been observed with use of antipsychotics. Monitor weight at baseline and frequently thereafter. In pooled data from placebo-controlled trials of adult patients with schizophrenia, mean changes from baseline and the proportion of patients with an increase in weight ≥7% from baseline to end of study was similar in patients treated with CAPLYTA and placebo. In an uncontrolled open-label trial of CAPLYTA for up to 1 year in patients with stable schizophrenia, the mean change in body weight was approximately -2 kg (SD 5.6) at Day 175 and approximately -3.2 kg (SD 7.4) at Day 350.

Leukopenia, Neutropenia, and Agranulocytosis: Leukopenia and neutropenia have been reported during treatment with antipsychotic agents, including CAPLYTA. Agranulocytosis (including fatal cases) has been reported with other agents in the class. Possible risk factors for leukopenia and neutropenia include pre-existing low white blood cell count (WBC) or absolute neutrophil count (ANC) and history of drug-induced leukopenia or neutropenia. In patients with a pre-existing low

WBC or ANC or a history of drug-induced leukopenia or neutropenia, perform a complete blood count (CBC) frequently during the first few months of therapy. In such patients, consider discontinuation of CAPLYTA 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 CAPLYTA in patients with absolute neutrophil count < 1000/mm³ and follow their WBC until recovery.

Orthostatic Hypotension and Syncope: Atypical antipsychotics cause orthostatic hypotension and syncope. Generally, the risk is greatest during initial dose administration. In these clinical trials the frequencies of orthostatic hypotension for CAPLYTA and placebo were 0.7% and 0%, respectively. The rates of syncope for CAPLYTA and placebo were 0.2% and 0.2%. Orthostatic vital signs should be monitored in patients who are vulnerable to hypotension (e.g., elderly patients, patients with dehydration, hypovolemia, and concomitant treatment with antihypertensive medications), patients with known cardiovascular disease (history of myocardial infarction, ischemic heart disease, heart failure, or conduction abnormalities), and patients with cerebrovascular disease. CAPLYTA has not been evaluated in patients with a recent history of myocardial infarction or unstable cardiovascular disease. Such patients were excluded from pre-marketing clinical trials.

Falls: Antipsychotics, including CAPLYTA, may cause somnolence, postural hypotension, and motor and sensory instability, which may lead to falls and, consequently, fractures and other injuries. For patients with diseases, conditions or medications that could exacerbate these effects, complete fall risk assessments when initiating antipsychotic treatment and periodically during long-term treatment. **Seizures:** Like other antipsychotic drugs, CAPLYTA may cause seizures. The risk is greatest in patients with a history of seizures or with conditions that lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in older patients.

Potential for Cognitive and Motor Impairment: CAPLYTA, like other antipsychotics, may cause somnolence and has the potential to impair judgment, thinking, and motor skills. In short-term (i.e., 4- to 6-week) placebo-controlled clinical trials of patients with schizophrenia, somnolence and sedation were reported in 24% of CAPLYTA-treated patients, compared to 10% of placebo-treated patients. Patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that therapy with CAPLYTA does not affect them adversely.

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

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

ADVERSE REACTIONS

The following adverse reactions are discussed in detail in other sections of the labeling: Increased Mortality in Elderly Patients with Dementia-Related Psychosis; Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis; Neuroleptic Malignant Syndrome; Tardive Dyskinesia; Metabolic Changes; Leukopenia, Neutropenia, and Agranulocytosis; Orthostatic Hypotension and Syncope; Falls; Seizures; Potential for Cognitive and Motor Impairment; Body Temperature Dysregulation; Dysphagia.

Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of CAPLYTA has been evaluated in 1724 adult patients with schizophrenia exposed to one or more doses. Of these patients, 811 participated in short-term (4- to 6-week), placebo-controlled trials with doses ranging from 14 to 84 mg/day. A total of 329 CAPLYTA-exposed patients had at least 6 months of exposure and 108 had at least 1 year of exposure to the 42-mg dose of CAPLYTA. There was no single adverse reaction leading to discontinuation that occurred at a rate of >2% in CAPLYTA-treated patients. The most common adverse reactions (incidence of at least 5% of patients exposed to CAPLYTA and greater than twice the rate of placebo) are somnolence/sedation and dry mouth. Adverse reactions associated with CAPLYTA (incidence of at least 2% in patients exposed to CAPLYTA and greater than placebo) are shown in Table 1. The following findings are based on the pooled short-term (4- to 6-week), placebo-controlled studies in adult patients with schizophrenia in which CAPLYTA was administered at a daily dose of 42 mg (N=406). Table 1 in the full Prescribing Information displays Adverse Reactions Reported in ≥2% of CAPLYTA-Treated Patients in 4- to 6-week Schizophrenia Trials. Adverse reaction is followed by percentage of patients treated with CAPLYTA 42mg (N=406) and Patients treated with Placebo (N=412) in parentheses. Somnolence/Sedation (24%, 10%); Nausea (9%, 5%); Dry Mouth (6%, 2%); Dizziness¹ (5%, 3%); Creatine Phosphokinase Increased (4%, 1%); Fatigue (3%, 1%); Vomiting (3%, 2%); Hepatic Transaminases Increased² (2%, 1%); Decreased Appetite (2%, 1%). ¹ Dizziness, dizziness postural; ² ALT, AST, "hepatic enzymes" increased, or liver function test abnormal.

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

Extrapyramidal Symptoms: In the 4- to 6-week, placebo-controlled trials, the frequency of reported events related to extrapyramidal symptoms (EPS), including akathisia, extrapyramidal disorder, muscle spasms, restlessness, musculoskeletal stiffness, dyskinesia, dystonia, muscle twitching, tardive dyskinesia, tremor, drooling, and involuntary muscle contractions was 6.7% for CAPLYTA and 6.3% for placebo. In the 4- to 6-week trials, data were collected using the Simpson Angus Scale (SAS) for EPS (total score ranges from 0 to 40), the Barnes Akathisia Rating Scale (BARS) for akathisia (total score ranges from 0 to 14), and the Abnormal Involuntary Movement Scale (AIMS) for dyskinesia (total score ranges from 0 to 28). The mean changes from baseline for CAPLYTA-treated patients and placebo-treated patients were 0.1 and 0 for the SAS, -0.1 and 0 for the BARS, and 0.1 and 0 for the AIMS, respectively.

DRUG INTERACTIONS

Table 2 in the full Prescribing Information displays Drugs Having Clinically Important Interactions with CAPLYTA. Moderate or Strong CYP3A4 Inhibitors: Concomitant use of CAPLYTA with moderate or strong CYP3A4 inhibitors increases lumateperone exposure, which may increase the risk of adverse reactions. Avoid concomitant use of CAPLYTA with moderate or strong CYP3A4 inhibitors. Examples of CYP3A4 inhibitors include: *Moderate inhibitors* - Amprenavir, ciprofloxacin, cyclosporine, diltiazem, erythromycin, fluconazole, fluvoxamine, verapamil. *Strong inhibitors* - Clarithromycin, grapefruit juice, itraconazole, voriconazole, nefazodone,

ritonavir, nelfinavir. **CYP3A4 Inducers:** Concomitant use of CAPLYTA with CYP3A4 inducers decreases the exposure of lumateperone. Avoid concomitant use of CAPLYTA with CYP3A4 inducers. Examples of CYP3A4 inducers include: Carbamazepine, phenytoin, rifampin, St. John's wort, bosentan, efavirenz, etravirine, modafinil, nafcillin, aprepitant, armodafinil, pioglitazone, prednisone. **UGT Inhibitors:** Concomitant use of CAPLYTA with UGT inhibitors may increase the exposure of lumateperone and/or its metabolites. Avoid concomitant use of CAPLYTA with UGT inhibitors. Examples of UGT inhibitors include: Valproic acid, probenecid

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Exposure Registry - There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to atypical antipsychotics, including CAPLYTA, during pregnancy. Healthcare providers are encouraged to register patients by contacting the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or online at <http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/>. **Risk Summary -** Neonates exposed to antipsychotic drugs during the third trimester are at risk for extrapyramidal and/or withdrawal symptoms following delivery. Available data from case reports on CAPLYTA use in pregnant women are insufficient to establish any drug associated risks for birth defects, miscarriage, or adverse maternal or fetal outcomes. There are risks to the mother associated with untreated schizophrenia and with exposure to antipsychotics, including CAPLYTA, during pregnancy. In animal reproduction studies, no malformations were observed with oral administration of lumateperone to pregnant rats and rabbits during organogenesis at doses up to 2.4 and 9.7 times, respectively, the maximum recommended human dose (MRHD) of 42 mg/day on a mg/m² basis. When pregnant rats were administered lumateperone during the period of organogenesis through lactation, the number of perinatal deaths of pups was increased at 4.9 times the MRHD, with no adverse effects on pups at 2.4 times the MRHD. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. **Clinical Considerations - Disease associated maternal and/or embryo/fetal risk:** There is risk to the mother from untreated schizophrenia, including increased risk of relapse, hospitalization, and suicide. Schizophrenia is associated with increased adverse perinatal outcomes, including preterm birth. It is not known if this is a direct result of the illness or other comorbid factors. **Fetal/neonatal adverse reactions:** Extrapyramidal and/or withdrawal symptoms, including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder have been reported in neonates who were exposed to antipsychotic drugs during the third trimester of pregnancy. These symptoms have varied in severity. Monitor neonates for extrapyramidal and/or withdrawal symptoms and manage symptoms appropriately. Some neonates recovered within hours or days without specific treatment; others required prolonged hospitalization. **Data - Animal Data:** Pregnant rats were treated with oral doses of 3.5, 10.5, 21, and 63 mg/kg/day lumateperone (0.8, 2.4, 4.9, and 14.6 times the MRHD on a mg/m² basis) during the period of organogenesis. No malformations were observed with lumateperone at doses up to 2.4 times the MRHD. Findings of decreased body weight were observed in fetuses at 4.9 and 14.6 times the MRHD. Findings of incomplete ossification and increased incidences of visceral and skeletal variations were recorded in fetuses at 14.6 times the MRHD, a dose that induced maternal toxicity. Pregnant rabbits were treated with oral doses of 2.1, 7, and 21 mg/kg/day lumateperone (1.0, 3.2, and 9.7 times the MRHD on a mg/m² basis) during the period of organogenesis. Lumateperone did not cause adverse developmental effects at doses up to 9.7 times the MRHD. In a study in which pregnant rats were administered oral doses of 3.5, 10.5, and 21 mg/kg/day lumateperone (0.8, 2.4, and 4.9 times the MRHD on a mg/m² basis) during the period of organogenesis and through lactation, the number of live-born pups was decreased at 2.4 and 4.9 times the MRHD, and early postnatal deaths increased at a dose 4.9 times the MRHD. Impaired nursing and decreased body weight gain in pups were observed at 4.9 times, but not at 2.4 times, the MRHD. Pregnant rats were treated with a human metabolite of lumateperone (reduced ketone metabolite) at oral doses of 15, 60, and 100 mg/kg/day (1.2, 19, and 27 times the exposure to this metabolite at the MRHD of lumateperone based on AUC plasma exposure) during the period of organogenesis. This metabolite did not cause adverse developmental effects at a dose 1.2 times the exposure at the MRHD of lumateperone; however, it caused an increase in visceral malformations (cleft palate) at 27 times and skeletal malformations at 19 times the exposure at the MRHD of lumateperone, a dose that induced maternal toxicity.

Lactation: Risk Summary - There are no available data on the presence of lumateperone or its metabolites in human milk or animal milk, the effects on the breastfed infant, or the effects on milk production. Toxicity in animals has been linked to the formation of aniline metabolites of lumateperone. Although aniline metabolites were not present in (adult) humans at quantifiable levels, it is unknown whether infants exposed to lumateperone will exhibit comparable lumateperone metabolism and elimination pathways as adults. In addition, there are published reports of sedation, failure to thrive, jitteriness, and extrapyramidal symptoms (tremors and abnormal muscle movements) in breastfed infants exposed to antipsychotics. Based on findings of toxicity in animal studies and the potential for serious adverse reactions in the breastfed infant, breastfeeding is not recommended during treatment with lumateperone.

Females and Males of Reproductive Potential: Infertility - Based on findings from animal studies, lumateperone may impair male and female fertility.

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

Geriatric Use: Controlled clinical studies of CAPLYTA did not include any patients aged 65 or older to determine whether or not they respond differently from younger patients. Antipsychotic drugs increase the risk of death in elderly patients with dementia-related psychosis. CAPLYTA is not approved for the treatment of patients with dementia-related psychosis.

Hepatic Impairment: Use of CAPLYTA is not recommended for patients with moderate (Child-Pugh class B) to severe hepatic impairment (Child-Pugh class C). Patients with moderate and severe hepatic impairment experienced higher exposure to lumateperone. No dosage adjustment is recommended for patients with mild hepatic impairment (Child-Pugh A).

OVERDOSAGE

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

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Traveling the Middle Road Between Skepticism and Scientism



Dan J. Stein, MBChB UCT, FRCP, PhD, DPhil, is professor and chair of the Department of Psychiatry at the University of Cape Town (UCT), Cape Town, South Africa. To avoid compulsory service in the all-white South African

army, he left for the United States, where he completed his residency in psychiatry and a postdoctoral fellowship in psychopharmacology at Columbia University. After Nelson Mandela was democratically elected president, Dr Stein returned to South Africa, where he has remained since. His research work has focused on anxiety and related disorders, including obsessive-compulsive and related disorders, and trauma- and stressor-related disorders. He chaired the DSM-5 and the ICD-11 workgroups on obsessive-compulsive and related disorders. Recognized for his contributions to multiple fields, he has received the Ethics in Psychopharmacology award from the International College of Neuropsychopharmacology and the Lifetime Achievement Award in Biological Psychiatry from the World Federation of Societies of Biological Psychiatry.

Dr Stein has been interested in both psychiatry research and philosophical writing since his residency. As a resident, he won the Karl Jaspers Award from the Association for the Advancement of Philosophy and Psychiatry in 1991. As part of the DSM-5 revision process, he wrote an article, collaborating with a number of leading figures in philosophy and psychiatry, titled "What is a mental/psychiatric disorder? From DSM-IV to DSM-V" that has been cited nearly 500 times.¹ In 2008, he brought together his interests in psychopharmacology and philosophy in *Philosophy of Psychopharmacology*, and this year he has further extended his work in philosophy with the publication of *Problems of Living: Perspectives from Philosophy, Psychiatry, and Cognitive-Affective Science*. This is an ambitious book, tackling questions not only about the nature of mental disorders, but also about the mind-body problem, the relationship between reason and emotion, happiness and suffering, morality and truth, and the meaning of life.

» Awais Aftab, MD

Conversations in Critical Psychiatry is an interview series that explores critical and philosophical perspectives in psychiatry and engages with prominent commentators within and outside the profession who have made meaningful criticisms of the status quo.

AFTAB: You are the first African author I have interviewed for this series. Does being South African influence your work on philosophy and psychiatry?

STEIN: Well, it is notable that South Africans have made some really important contributions to psychiatry. The work of Joseph Wolpe, MD, developing behavior therapy comes to mind, as does Isaac Marks, MD's contribution to anxiety disorders (others are detailed in a review I once wrote).² On the other hand, critiques of psychiatry have had particular resonance here, emphasizing how social determinants and health systems are closely bound up with the history of apartheid and continue to influence mental health.

AFTAB: Your specific interest in the philosophy of psychopharmacology distinguishes you from many other authors and commentators in this area. Psychopharmacology too is a field where there have been advances but also important limitations.

STEIN: Yes, I fully agree. The introduction of antipsychotics, antidepressants, anxiolytics, and mood stabilizers in the 20th century was a complete game-changer for psychiatry. At the same time, the same receptors targeted by early agents continue to, by and large, remain the focus of current clinical psychopharmacology. Neuroscience has become increasingly sophisticated, and yet our understanding of how psychotropics affect symptom relief remains somewhat rudimentary. We should celebrate the fact that appropriate diagnosis and pharmacotherapy changes many individuals' lives for the better. But we must remain aware that there is massive underdiagnosis, particularly in low- and middle-income countries, that not all patients respond to pharmacotherapy or other interventions, and that overdiagnosis and

overtreatment is also an issue.

AFTAB: Selective serotonin reuptake inhibitors (SSRIs) and other antidepressant medications have been the subject of a lot of controversy in recent years. There is the perpetual question: Why have they performed so poorly when compared to placebos in randomized controlled trials (RCTs), and what does that say about their real-world clinical efficacy? And there is increasing awareness of the prevalence and severity of antidepressant withdrawal and other adverse effects. As someone who approaches psychopharmacology through a philosophical lens, how do you view these developments?

STEIN: In my thinking about these sorts of issues in psychopharmacology and related questions in philosophy of psychiatry, I find myself always trying to walk the line between overly hagiographic accounts and overly critical views of psychiatry. When I think of how psychotropics can impact thinking and feeling, and be so therapeutic, I am filled with awe (about the complexity of the relevant mechanisms) and with gratitude (that we are able to help individuals suffering from mental disorders). But I am also very aware of the robust criticisms of psychopharmacology's evidence base, of iatrogenic illness, and of how far we still have to travel in psychopharmacology. I don't think there's a deep and readily addressed conceptual solution in psychopharmacology research. We have long been aware, for example, that neurotransmitters cut across dimensions of behavior, and that, while psychopharmacological dissection may be a useful tool, the idea that there is going to be a specific psychotropic that is particularly effective for each disorder is way too simplistic.

I do think, though, that in clinical practice it may be helpful to think about psy-

chopharmacology not only from a molecular perspective but also from an evolutionary medicine perspective. This helps explain why anxiety is so common, why there are endogenous anxiogenic and anxiolytic mechanisms (which we can then target or mimic), why medications that target adaptive defenses can be clinically useful (an antitussive can reduce symptoms even though cough is highly adaptive), and why the motto “a pill for every ill” is far from the solution.

From a research perspective, while I love the current idea that clinical trials can be based on translational neuroscience approaches (eg, testing if a drug alters an important biomarker or endophenotype), successful bench-to-bedside advances remain fairly unusual in psychiatry, and I worry that we do not put commensurate attention and funding into pragmatic clinical trials. The United Kingdom’s Recovery Trial to quickly test drugs for efficacy against COVID-19 in day-to-day practice is inspiring. Should we not be doing the same sort of thing for mental disorders?

AFTAB: You have often differentiated among the *classical*, *critical*, and *integrative* positions. Tell us a bit more about these, particularly as you envisage them with regards to psychiatry.

STEIN: I have used these terms in part to find a middle path, avoiding both overly hagiographic and overly critical views of psychiatry and psychopharmacology. I have also used them as a way of integrating key philosophical views on science, language, and medicine. Thus, I use the term *classical* to refer to positions that emphasize essential natural kinds and scientific laws, holding up, say, the periodic table as an example of how science should work, and arguing that diseases too have essential features, which we need to explain. And I use the term *critical* to refer to positions that emphasize social construction and hermeneutic methods, pointing out that our concepts vary from time to time and place to place, arguing that mental disorders are socially constructed, and that the experience of being ill needs to be understood. I try to put forward an *integrative* approach which avoids the scientism of the classical view and the skepticism of the critical view, and which sees psychiatric science as both a social activity and a powerful account of the structures, processes, and mechanisms underlying phenomena, including disorders.

AFTAB: Your most recent volume is *Problems of Living*. Would you like to introduce the book to the readers in your own words? What are some of the major themes and conclusions of the book?

STEIN: It has been more than a decade since I wrote *Philosophy and Psychopharmacology*, and I have been wanting to get back to thinking about philosophy and psychiatry. I see the volume as expanding on my earlier work in a few key ways. First, whereas my earlier volume was on psychopharmacology, here I draw on a whole range of

different scientific findings about the brain-mind. Second, my earlier volume spoke mainly about scientific naturalism and explanatory pluralism, but here I expand more on moral naturalism and value pluralism. Third, my earlier volume spoke mainly to the philosophy and ethics of psychopharmacology, whereas here I expand to cover the philosophy and ethics of a range of aspects of human life, including the question of the meaning of life. There are also key continuities between the volumes. The possibility of a middle way, of a balanced approach, remains a central issue for me, and I hope the volume is useful for readers also interested in that kind of path.

Given my interest in embodied cognition, I am very aware that expressions such as “a middle way forwards” and “a balanced approach” employ metaphors. My last chapter in *Problems of Living* is a brief reflection on the metaphors we use for thinking through life, the big questions and hard problems that it raises, and ultimately its meaning. I suggest that the metaphor of life as a journey may be a particularly useful one, and I spend some time on fleshing it out, and encouraging a course that avoids both unbridled optimism and relentless pessimism. It is a bit whimsical in spirit, but I hope it appeals to at least some readers.

AFTAB: You use the notion of *wetware* to talk about brain-minds. Can you tell us more about it and what you see as the advantage of employing this metaphor?

STEIN: The mind-body problem includes the hard problem of consciousness, and key philosophical positions include physicalism, dualism, and functionalism, which relies in part on the hardware-software distinction in cognitive science. We increasingly use the hardware-software metaphor in everyday life, as well as in psychiatry. It is easy for us to talk about medications as changing our hardware, and psychotherapy as changing our software. But while brain-as-thinking-machine metaphors can be useful, they also lead to important errors: psychiatry needs to remain vigilant and avoid brainless and mindless approaches. For me, the term *wetware* helps emphasize how the brain-mind (a term I think we should use more often) is biological through and through, with cognitive-affective phenomena embodied in brain processes and embedded in social activity.

AFTAB: At one point you write, “What about the fact that much psychotherapy is aimed not at

specific mental disorders, but rather at ‘problems of living’? Can we really make progress in providing help for this sort of issue?”⁴ I think you are right that a lot of psychotherapy is aimed at problems of living, but it seems to me that a lot of contemporary pharmacotherapy is also aimed at problems of living, especially the use of SSRIs in primary care settings for the treatment of depression, anxiety, stress, etc. According to the Centers for Disease Control and Prevention, between 2015 and 2018, 13% of American adults were prescribed an antidepressant medication.⁵ It just does not seem that way because we are able to hide the distress and impairment behind all sorts of diagnostic labels. I am not taking the extreme Szaszian view here that all psychiatric disorders are problems of living, but more of a gentle skeptical view that there is no natural distinction to be found. Would you agree with that?

STEIN: Your point that both psychotherapy and pharmacotherapy address problems of living is a trenchant one. And I am with you with regards to a gentle skeptical view that there is a spectrum from psychiatric disorders through to problems of living, and my sense is that this is increasingly recognized both in neuroscience (eg, in the Research Domain Criteria framework) and in global mental health (which often speaks of the spectrum from illness to health). In *Problems of Living*, I often turn to Aristotle. I trust we are better at treating bipolar disorder than the ancient Greeks, but I suspect that the ancient Greeks were as good as helping individuals with problems in human relationships as we are, demonstrating the sort of practical wisdom (*phronesis*) that is required in medicine and psychiatry. Although advances in obsessive-compulsive disorder inspired me to go into that field,

and, although I am proud of the ongoing progress the field has made, I suspect that Aristotle and his physician father would have some good techniques up their sleeves to manage some quite serious mental illnesses. Certainly, Aristotle’s thinking about mental disorders is sometimes very prescient.

AFTAB: As I was reading your discussion of metaphors, I thought of a quote by Derek Bolton, PhD, and Grant Gillett, MSc, DPhil, from their book on the biopsychosocial model. They write at one point: “What is missing from and obscured by these two-dimensional picture metaphors of levels and nested domains is the temporal, evolutionary and developmental,



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parameter...no static metaphor, whether in terms of levels or nested systems, capable of being drawn on a page, does justice to the new systems sciences, which essentially invoke dynamical interaction in present time, on the basis of co-evolution through deep time.”⁶

I think this shows us the power of metaphors to constrain us as well as liberate us. Our historical understanding of biopsychosocial complexity has been constrained by static metaphors, while new metaphors (such as baking a cake as a metaphor for organizational causality by Sanneke de Haan, PhD) free us from old mechanical ways of thinking. What is your view on the use of metaphors in philosophy and psychiatry?

“Despite its important limitations, psychiatry does have extraordinary breadth and depth, I would argue that our field does already exemplify explanatory pluralism, and that a good clinician is necessarily taking an integrative approach.”

STEIN: Dr Bolton co-supervised my dissertation in philosophy, and I am a fan of his work as well as of enactive approaches to psychiatry. I fully agree with your view that metaphors can constrain as well as liberate us. I have been interested in how metaphors work in our distinctions between typical and atypical disorders. In a typical disorder, metaphors such as being *attacked* work well: someone with pneumonia is attacked by a bug, we fight back with a drug, and they are not blamed but rather deserve the sick role. However, in an atypical disorder, these metaphors work less well: someone with alcoholism is not simply attacked by an external agent, rather they have to take some responsibility for their illness, and there is debate about the extent to which they deserve the sick role. It is as if we shift from medical to moral metaphors for conditions such as alcoholism. So, I like the idea of metaphors of addiction that bridge the medical and moral in order to avoid blame but also to emphasize responsibility.

AFTAB: Your experiences with professors of psychoanalytic orientation vs those of neurobiological and nosological orientation during your psychiatric residency seem to have left a deep mark on you. The notable schisms that I think our field is confronting now are between quite different players. Schisms between so-called *evidence-based* technological approaches (pharmacotherapy, CBT, etc) vs existential-humanistic-psychodynamic approaches; biomed-

ical models vs interpersonal-relational models; and the epistemic authority of medical professionals vs epistemic authority of users of psychiatric services (exemplified by movements such as neurodiversity, mad pride, service user/survivors/ex-patients, etc). My approach to these schisms is in alignment with the same pluralistic and integrative approaches that you adopt.

However, a concern increasingly comes up when I discuss these things: within a pluralistic-integrative framework integrating these polarities, it is no longer obvious that psychiatry as a medical profession—that has increasingly specialized in psychopharmacology and clinical

neuroscience over the last 3 decades—serves as the suitable umbrella profession for the integrated domain, instead of, say, clinical psychology, or social work, or even efforts led by service users. If neuroscience and psychopharmacology will no longer be of central importance in the new pluralism (at least it's not obvious), then why should psychiatry continue to claim its existing power?

STEIN: I agree with you about the importance of the schisms that you mention (my sense is that these partly reflect aspects of the biological-psychoanalytical schism), and I am glad that you are in alignment with pluralistic and integrative approaches to address them.

In *Problems of Living*, I emphasized the importance of epistemic humility and of owning our fallibility; so absolutely we need to be open to entirely new ways of explaining, understanding, and improving mental health. Certainly, mental health care is too important to be left solely to psychiatrists. My work on trichotillomania has clearly taught me how much service users know, and how valuable they are in creating solutions.

At the same time, I would want to appropriately acknowledge the breadth and depth of psychiatry. So, with regard to sharing hegemony, I may be a bit more conservative than you would like. In my book, I refer a few times to the work of Jonathan Haidt, PhD, who, as you know, has

argued for diversity of political positions; I do wonder if greater balance between conservatism and progressivism in general may not be useful, as we move forwards.

AFTAB: What do you see as some of the challenges we face in the pursuit of an integrative and pluralistic approach to psychiatry, and how can psychiatrists, especially trainees, better prepare for these challenges ahead?

STEIN: Another great question. From your columns I know you have a knack for making thinkers think harder. In line with my view that despite its important limitations, psychiatry does have extraordinary breadth and depth, I would argue that our field does already exemplify explanatory pluralism, and that a good clinician is necessarily taking an integrative approach. I do think that explicitly providing residents conceptual frameworks, as you have advocated for, is a good idea; this might be useful in seeing the explanatory pluralism we use as something to be proud of rather than concerned by. I also think that explicitly providing residents with exposure to good clinicians and researchers, who are able to explain how they integrate different ideas and approaches, is useful.

Finally, although I appreciate that it is important to be hopeful about the future, I also think that more explicit humility might be helpful at times; in our understandable zeal to address suffering, we may run the risk of overselling what we can do with any particular treatment approach, or any particular research program. In sum, I go back to a favorite metaphor: a balanced approach is key!

The opinions expressed in the interviews are those of the participants and do not necessarily reflect the opinions of *Psychiatric Times*™.

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Personality Disorder and Dangerousness

Najat R. Khalifa, MD; and Philip J. Candilis, MD

Driven by a mandate to protect the public, many Western jurisdictions call upon psychiatrists, particularly forensic specialists, to evaluate dangerousness in individuals with mental disorders. Such evaluations occur for civil and criminal proceedings, bail and parole determinations, and hospital and emergency department discharges.¹⁻³ While risk assessment has become a relatively uncontested part of criminal proceedings in places like the United States and the United Kingdom (UK), the influence of expert testimony on civil commitment, guardianship, sentencing or release, and the attendant civil liberties require a careful look at the accuracy and reliability of expert assessments,³ especially among the prevalent but commonly misunderstood personality disorders.⁴

This article examines the empirical literature on the link between personality disorders and dangerousness, the limitations inherent in using risk assessment tools to verify the link, and the ethical

issues surrounding the assessment.

What Is a Personality Disorder?

The *DSM-5* defines personality disorder as “an enduring pattern of inner experience and behavior that deviates markedly from the expectations of the individual’s culture, is pervasive and inflexible, has an onset in early adolescence or early adulthood, is stable over time and leads to distress or impairment.”⁵

This definition attests to the pervasive, persistent, and problematic nature of the disorder, not just how the individual is currently presenting. *DSM-5* recognizes 10 types of personality disorder (apart from personality disorder not otherwise specified).⁵ These are classified into 3 well-known clusters: Cluster A (paranoid, schizoid, schizotypal); Cluster B (antisocial, borderline, histrionic, narcissistic); and Cluster C (avoidant, dependent, obsessive-compulsive).

Five major epidemiological studies in the

United States showed overall prevalence rates of around 10% for any personality disorder.⁶ The comprehensive National Comorbidity Study Replication reported a past-year prevalence of 9.1% for any personality disorder among adults 18 years and older.⁷ The most common personality disorder was the avoidant type (5.2%), followed by schizoid (4.9%), schizotypal (3.3%), obsessive-compulsive (2.4%), paranoid (2.3%), borderline (1.6), antisocial (1.0%), and dependent (0.6%). The study recorded no cases of histrionic or narcissistic personality disorders. Although the National Epidemiologic Survey on Alcohol and Related Conditions did not report an overall prevalence rate for personality disorders, it did identify higher rates for histrionic (1.8%)⁸ and narcissistic (6.2%) personality.⁹

In contrast, European studies report lower prevalence rates. For instance, the British household survey of more than 8000 respondents found a prevalence rate of 4.4% in the general popula-

ACTIVITY GOAL

The goal of this activity is to update readers about the putative link between personality disorder and dangerousness.



LEARNING OBJECTIVES

1. Understand 3 cardinal elements contributing to legal definitions of dangerousness (namely, danger to self or others, inability to care for self, and, potentially, the need for treatment), and describe the empirical link between Cluster B personality disorders and violence.
2. Identify 3 limitations inherent in using risk assessment tools to verify the link between personality disorder and dangerousness (namely, categorical *DSM* classifications, the influence of social norms, and the redundancy of definitions that include aggression).

TARGET AUDIENCE

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

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tion, with higher rates being reported in men, the unemployed, those who were separated or divorced, and those living in urban areas.¹⁰

Notwithstanding variations in prevalence, personality disorders, particularly antisocial personality disorder (AsPD), exact a substantial health and economic burden, affecting health service utilization, unemployment, criminality, suicidality, and homelessness.¹¹ AsPD has particularly strong effects on violence.¹⁰

What Is Dangerousness?

One challenge to linking personality disorder to dangerousness is that no universally accepted definition exists, although some commentators distinguish clinical and legal dangerousness.¹² An early definition of clinical dangerousness regarded it as “a propensity to cause serious physical injury or lasting psychological harm.”¹³ More recent definitions are mainly legal, so they vary across jurisdictions. A notable exception intended to assess and treat individuals with Dangerous and Severe Personality Disorder (DSPD) is the UK’s DSPD Program, launched in 2001 in 2 high-security prisons and 2 high-security forensic hospitals. An individual was classified as having DSPD if they showed evidence of both dangerousness (defined as a high risk of harm to others) and severe personality disorder, as well as a functional link between the 2. Severe personality disorder was operationalized as high scores (25 or above) on the well-established Psychopathy Checklist–Revised, in conjunction with at least 1 personality disorder other than antisocial, or 2 or more personality disorders.^{14,15} The program was a costly one that catered to the needs of only a few hundred individuals with DSPD who were detained in maximum security. There was little or no provision for those living in the community. It was eventually ended in favor of a new community-based strategy for managing personality-disordered offenders. The new strategy adopted a whole-systems approach across the criminal justice and health systems, recognizing the various stages of an offender’s journey from sentence through community reintegration.¹⁶

Legal definitions tend to be prescriptive. For example, in the United States, the evolution of dangerousness is most clearly seen in statutes on civil commitment, where dangerousness ultimately replaced illness as a standard for hospitalizing individuals against their will.^{17,18} Often traced back to the passage in the District of Columbia of the influential Ervin Act of 1964 (an early piece of influential legislation named for US Senator Sam Ervin of Watergate fame), dangerousness usually required an imminent threat, generally interpreted as physical harm to oneself or others. A right to treatment based in the US Constitution’s due process clause never materialized. Many states instead followed the District’s commitment model, emphasizing the specific link between mental illness and danger. The US Supreme Court ultimately underscored the risk of harm, adding the inability to care for oneself and intimating that treatment may be required as well.¹⁹

Table 1. Three Broad Categories of Violence Risk-Assessment Tools

Category	Features
Unstructured clinical	Intuitive professional judgment based in clinical experience
Structured professional judgment	Systematic application of a professional’s knowledge of context and empirical data
Actuarial	Use of validated tools or algorithms using statistical associations of risk factors and violence

Under the UK’s Criminal Justice Act 2003, an offender is classified as dangerous “if the court is of the opinion that there is significant risk to members of the public of serious harm occasioned by the commission by him of further specified offenses.”²⁰ A “specified offence” is a violent, sexual, or terrorism offense, and “serious harm” means “death or serious personal injury, whether physical or psychological.”²⁰

A consideration common to most legal definitions is that dangerousness is a relatively stable attribute of the individual,¹² although scientific evidence shows that human behavior is influenced by a complex interplay of individual and environmental factors.²¹ This is a conflict that calls for a comprehensive clinical assessment for any individual facing a concern for violence, including a review of protective factors.

Assessment of Dangerousness

Current approaches to assessment of dangerousness rely on violence (including sexual) risk assessment tools, which fall into 3 broad categories (**Table 1**): unstructured clinical, actuarial, and structured professional judgment. While the unstructured clinical approach performs better than chance in predicting future violence, it has been criticized for lacking reliability and validity.²²

Actuarial approaches rely heavily on static (unchangeable) risk factors (ie, sex, prior offenses, age at release) and provide probabilistic estimates of the risk of future violence within a specified time period.²³ Actuarial approaches have been criticized for leaving no room for clinical discretion and for relying on factors that are not amenable to change.²⁴ Additionally, their accuracy in predicting rare events has been contested because they rely on information derived from group data to assess risk for an individual.³

Structured professional judgment approaches rely on a constellation of actuarial and dynamic (changeable) risk factors that have been empirically associated with future violence. While they help bridge the gap between clinical and actuarial approaches, structured judgments are resource intensive and their predictive value is often less than robust.²⁴

While each approach has its advocates and critics, none is wholly satisfactory.¹² A problem common to actuarial and structured professional judgment is the difficulty inherent in predicting a behavior with a low base rate. To illustrate the point, Singh et al reported significant variations in actual rates of violence in individuals identified as high risk by structured instruments, likely due to failure to account for local base rates for violence.²⁵

Although collateral information about violence rates in the geographic area may be useful, the issue of how to obtain and incorporate this information into risk assessments is yet to be determined.

Another problem is the variability in predictive accuracy of these tools. In 74 samples totalling 24,847 individuals, for example, Fazel et al assessed the predictive validity of the 9 most commonly used tools assessing the risk of violence, sexual, and criminal behavior (**Table 2**).²⁶ The authors reported that although violence risk-assessment tools performed better than those designed to predict sexual and general offending, they had a median predictive value of only 41% with a corresponding median number needed to detain of 2 (range, 2-4). The evidence did not support the use of these tools as sole determinants of decisions related to detention, sentencing, and release.

Similarly, Buchanan and Lesse reported on the sensitivity and specificity of actuarial and structured tools used to predict future violence among adults in the community.²⁷ They reported a mean sensitivity of 0.52 (essentially a coin toss) and mean specificity of 0.68; the corresponding number needed-to-treat for these tools was 6. These are hardly encouraging numbers for assessments that carry significant dangers of detention, stigma, and criminalization.

What is the Link?

The association between personality disorders, particularly Cluster B, and violence is well-documented.^{28,29} For example, the British Household Survey found that individuals with a Cluster B personality disorder were 10 times more likely than those without to have a criminal conviction, whereas individuals with a Cluster A or C personality disorder were no more violent than the general population.³⁰ Indeed, Yu et al reported an odds ratio of violence of 12.8 for those with AsPD compared with the general population.²⁸

Despite the association between some personality disorders and violence, the mechanisms which mediate the link remain poorly understood. Any analysis must begin with the distinction between risk and causal factors. A risk factor is one that consistently predicts an outcome, while causality requires that certain criteria are actually met. These criteria are (1) covariance between the predictor and outcome (a measure of how much 2 factors vary together); (2) temporal precedence (ie, the predictor preceding the outcome); (3) exclusion of other plausible explanations; and (4) a logical connection between the predictor and outcome.³¹

In applying these criteria to the relationship between personality disorder and violence, Dug-

Table 2. 9 Risk Assessment Tools²⁶**ACTUARIAL INSTRUMENTS:**

Level of Service Inventory – Revised (LSI-R)
 Psychopathy Checklist – Revised (PCL-R)
 Sex Offender Risk Appraisal Guide (SORAG)
 Static-99
 Violence Risk Appraisal Guide (VRAG)

STRUCTURED CLINICAL JUDGMENT TOOLS:

Historical, Clinical, Risk Management-20
 (HCR-20)
 Sexual Violence Risk-20 (SVR-20)
 Spousal Assault Risk Assessment (SARA)
 Structured Assessment of Violence Risk in
 Youth (SAVRY)

gan and Howard found no unequivocal evidence to support a causal relationship, emphasizing the need to specify an understandable mechanism by which the disorder causes violence.⁴ They suggested that other variables like comorbidity with both *DSM-IV* Axis I and II may mediate the relationship.

However, a major obstacle to research and analysis is the problem inherent in the assessment and diagnosis of personality disorder itself. Current psychiatric classification systems like the *DSM-5* are categorical and heavily influenced by prevailing social norms, whereas personality traits are dimensional in nature.¹² This means that categorical measures of personality disorder are of limited validity, and that diagnosis may vary from one assessment method to another.³² This distinction between approaches (whether conditions fit neatly into a category or along a spectrum) continues to confound diagnosis because conditions overlap and differ in their range of impairment and severity. The *DSM* itself in 2013 described dimensionality as an emerging model, encouraged further research, and included dimensional approaches alongside the traditional categorical approach.

Another obstacle is the issue of circularity or redundancy.⁴ This arises because the diagnostic criteria for some Cluster B personality disorders include attributes that are already associated with criminality, namely aggression, anger outbursts, hostility, impulsivity, and callousness. The relationship between personality and violence is further confounded by comorbidity. Individuals with personality disorder typically present with more

than 1 personality disorder, as well as other common disorders such as substance misuse, depression, and anxiety.^{33,34} Similarly, personality disorders, particularly cluster B, are highly prevalent among individuals with substance use disorders, with an overall prevalence rate of 56.5% reported among patients treated for addictions.³⁵ These may all contribute to violence risk and further confound the link between personality disorder and violence.

A commonly reported comorbidity in forensic populations is the co-occurrence of antisocial and borderline personality disorders, alongside psychopathy. This has been linked to a wide range of antisocial outcomes, including both the severity and versatility of violent offending, as well as substance misuse.^{36,37}

A persistent conundrum is the mechanism through which personality disorder, including personality comorbidity, is linked to violence. It has been suggested that factors linking personality disorder to violence may include emotional dysregulation, deficits in self-regulation, early-onset alcohol abuse (18 years or younger), and impulsivity.³⁸⁻⁴⁰ Influential factors can be protective as well, since some have been associated with desistance from crime. These include employment, marriage, association with prosocial peers, developing prosocial values and behaviors, and others.⁴¹

Ethical Issues

Beyond matters of scientific uncertainty, the ethics of working where psychiatry and the law overlap is bound to give rise to tensions between safety and liberty, and between the individual and the community. Denying one's liberty on the grounds of a clinical opinion (diagnosis) couched in legal language (dangerousness) goes well beyond definitional uncertainties. Practitioners must be explicit about their inferences and opinions because the patient's best interest matters to both law and psychiatry.³ At the same time, the community's safety is a time-honored consideration as well. Balancing these influences is neither a medical nor legal exercise alone.

The traditional ethics question posed to psychiatrists assessing violence risk is this: Do they serve medicine or the law? Newer perspectives on forensic agency take views that advocate more clearly for the dignity of individuals and the professionalism of practitioners when pitting vulner-

able patients against large social systems.^{42,43} It is important to remember that patients require support and advocacy when facing assessments that threaten their freedom, including appropriate informed consent and robust warnings on the limits of confidentiality.

Risk assessment itself is bound to raise ethical issues. As neither a medical nor psychological concept, it is not yet an exact science. There is disagreement about ethical values and what constitutes a risk to the community. There may be differences between professionals like judges and physicians, between professionals taking an actuarial or structured approach, and between plaintiffs and defendants. These are the tensions of an evolving science that incorporates medical, legal, and psychological concepts all at once (**Table 3**). Sadly, the community retains unrealistic expectations that psychiatrists can protect society with accurate assessments of rare events like physical or sexual violence.³

Concluding Thoughts

Although the link between some personality disorders and violence is well documented, much still remains to be learned about the factors that mediate the link. Indeed, some of these factors may be outside the sphere of medicine. The limitations are therefore manifold.

First, current measures of personality disorder are of limited validity and are heavily influenced by prevailing social norms.

Second, dangerousness is neither a medical nor psychological concept. It is primarily legal and varies across jurisdictions.

Third, current assessment tools are far from perfect. Certainly, the current evidence suggests that their use as sole determinants of dangerousness is fraught with difficulty.

Fourth, professional ethics require acknowledging the uncertainty of scientific methods, methods that enter a social forum like the courts where nonmedical standards of morality and culpability apply.

Finally, a determination of dangerousness carries a heavy stigma for the individual concerned, alongside the potential denial of liberty.

Ultimately, risk assessments are more appropriately conducted as part of a broader clinical process aimed at developing risk management plans for high-risk groups.^{3,26} For individual assessments, they require robust informed consent, warnings on the limits of confidentiality, and a strong understanding of low base-rate phenomena and the jurisdiction's definition.

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Table 3. Practical Tips for Individual Assessments of Risk of Violence or Sexual Offending

1. Obtain informed consent after advising the individual on the purpose of the assessment and the limits of confidentiality.
2. Use validated tools to diagnose personality disorder, incorporating patient self-report, clinical observations, and collateral information.
3. Use validated tools for assessing the risk of violence or sexual offending.
4. Present a balanced argument in your documentation, highlighting protective factors as well as risk.
5. Remember that in both civil and criminal proceedings, dangerousness is ultimately a matter for the court.

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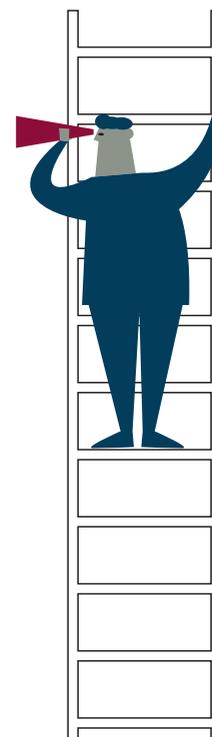


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Office of
Mental Health

Buffalo
Psychiatric Center

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.

About the Buffalo Area:

WNY has a superb quality of life. Buffalo and its surrounding suburbs have among the most affordable housing in the nation. Sports enthusiasts enjoy major and minor league teams and the metropolitan area is a mecca for history, architecture, art, and dining. WNY is home to excellent public and private schools, numerous top-tier universities and a well-renowned medical corridor comprised of the region's premier health care, life sciences, research, and medical education institutions. The Buffalo-Niagara area offers a plethora of outdoor activities including skiing, hiking, and boating.

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 Idemnification; broader in scope than typical malpractice coverage
- Academic affiliations with a number of prestigious institutions
- Salary Range: \$244,212 - \$283,241



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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.



Office of
Mental Health

Buffalo
Psychiatric Center

The Buffalo Psychiatric Center, located in Buffalo, NY, is seeking Psychiatrists for Inpatient and Outpatient services.

Applicants must be Board Certified or Board Eligible in psychiatry. Excellent benefits including medical/dental/vision insurance; generous paid time off; defined benefit retirement plan; continuing education plan; loan repayment program; and opportunity to earn additional salary. Western NY offers affordable housing; major league sports teams; world class theaters, restaurants, and a philharmonic orchestra; close proximity to Niagara Falls; a beautiful waterfront; and numerous colleges and universities.

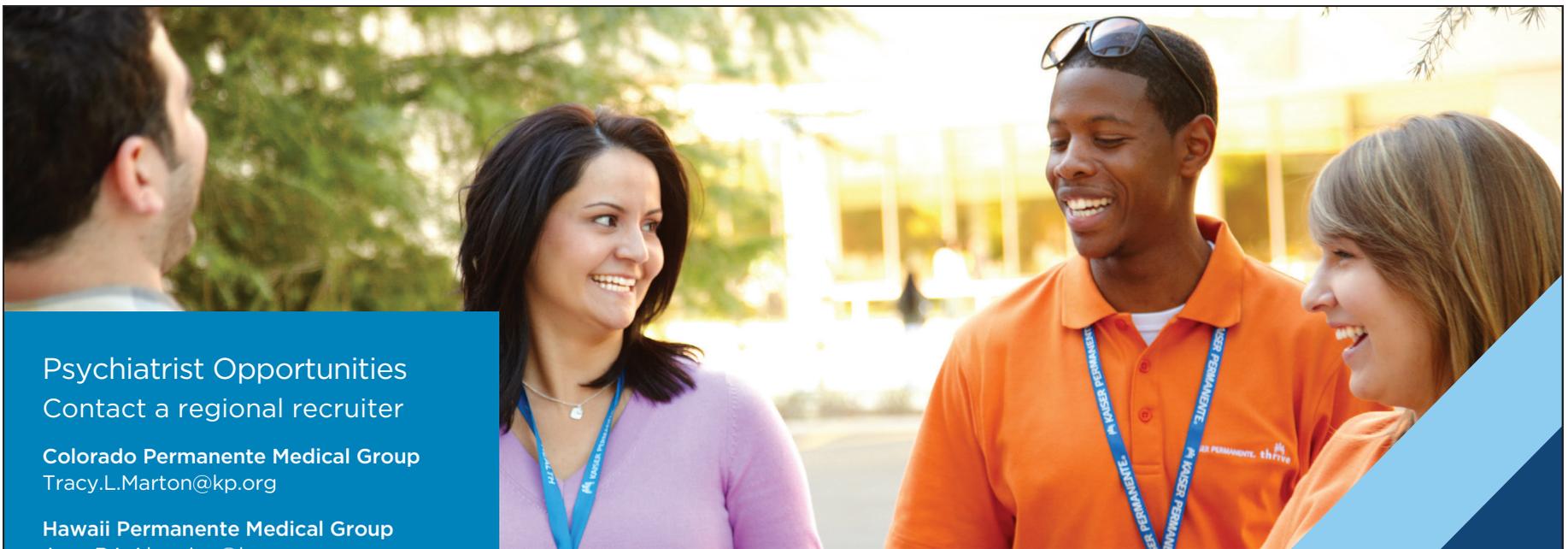
Applicants interested in positions at BPC, please forward your CV to:

Buffalo Psychiatric Center
Human Resources
400 Forest Avenue
Buffalo, NY 14213

716-816-2554 (fax); or

BPC-Careers@omh.ny.gov

BPC is an AA/EOE



Psychiatrist Opportunities
Contact a regional recruiter

Colorado Permanente Medical Group
Tracy.L.Marton@kp.org

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Jason.R.Dulin@kp.org

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Practicing Permanente Medicine means
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UMass Memorial Health and the University of Massachusetts Medical School currently have openings within the Department of Psychiatry.

The Department of Psychiatry is a national leader in addiction, biological, child and adolescent, and public sector, psychiatry, neuropsychiatry, psychosocial rehabilitation, and women's mental health. We integrate our clinical, research, teaching and community partnership activities to help individuals and families transform their lives through recovery from mental illness and addiction. We are the largest provider of psychiatric services in central Massachusetts, with over 400 faculty members and 12 hospitals and community mental health centers in varied settings across the state, from urban clinics to beautiful shore-side facilities such as Cape Cod.

Our residency program trains 7 residents per year, including general psychiatry and specialty tracks for combined adult and child psychiatry and combined psychiatry and neurology. We offer fellowships in Addiction, Adult Developmental Disabilities, Child and Adolescent, Forensic Psychiatry, and Neuropsychiatry.

Diversity, equity, and inclusion are integral to the commitment of the Department and University. Accordingly, the Department seeks qualified candidates who can contribute to racial equity, diversity and inclusion through service, mentorship, teaching and scholarship. Further, the Department is keenly interested in diversifying its faculty and staff and encourages applications from diverse candidates. Candidates from historically under-represented group(s) in higher education and medicine are encouraged to apply. Candidates who possess personal characteristics that might be considered as diversifying elements among the clinical team and the larger psychiatry faculty at UMMS are invited to identify themselves during the application process.

UMass Medical School

Facility Medical Director (Brockton Multi-Service Center, Brockton, MA)
administration and direct care for DMH contracted outpatient clinic and community support programs.

Full-Time Psychiatrist (Brockton Multi-Service Center, Brockton, MA)
Outpatient services.

Full-Time Psychiatrist (Worcester Recovery Center and Hospital, Worcester, MA)
2 new inpatient positions for WRCH expansion.

Child & Adolescent Psychiatrist (Worcester Recovery Center and Hospital, Worcester, MA)
Inpatient adolescent care units

Forensic Psychiatrist (Worcester Recovery Center and Hospital, Worcester, MA)
Inpatient Evaluation and Treatment.

Geriatric Researcher, Psychologist/Psychiatrist (UMMS, Worcester, MA)

FOR ADDITIONAL INFORMATION ON THE ABOVE, PLEASE CONTACT:
Marie Hobart, MD, Vice Chair, Public Sector Psychiatry
marie.hobart@umassmed.edu

Interested applicants should apply directly at
<https://academicjobsonline.org/ajo/UMASSMED/Psych>
(J-1 and H-1B candidates are welcome to apply)

UMass Memorial Health Care

Attending Psychiatrist Women's Health, OPD (Worcester, MA)
provide opportunities for integrating mental health care into obstetric settings through education, consultation, and telepsychiatry

Associate Medical Director, CHL (Worcester, MA)
Provide psychiatric and medical supervision

General Adult Outpatient Psychiatrist, CHL (Worcester, MA)
Outpatient evaluation, consultation and treatment, collaborating with other providers.

Child Psychiatrist CL, (Worcester, MA)
Provide consultation and liaison services to our pediatric ward at the Children's Medical Center and emergency mental health department.

Attending Geriatric Psychiatrist (Worcester, MA)
provide outpatient Geriatric Psychiatry and Innovative Consultation to Primary Care.

Interested applicants should submit a letter of interest and curriculum vitae addressed to
Kimberly Yonkers, MD: c/o: Jessica Saintelus, Physician Recruiter
Jessica.Saintelus@umassmemorial.org

<http://jobs.jobvite.com/umassmemorialmedicalgroupphysicians/search?q=&d=Psychiatry>

As the leading employer in the Worcester area, we seek talent and ideas from individuals of varied backgrounds and viewpoints.

PSYCHIATRISTS

For clinical staff and leadership positions

The State of New Jersey's Division of Behavioral Health Services is seeking motivated Psychiatrists for full-time inpatient work in our Joint Commission accredited State psychiatric hospitals and forensic center. Psychiatrists with management experience are also needed to serve as Chiefs of Psychiatry.

Post Certified - \$260,651 (3+ years post certification)
Board Certified - \$242,369
Board Eligible - \$228,561

- Facilities are in close proximity to metropolitan centers of New York City and Philadelphia/N.J. Shore
- Psychiatrists work with a multidisciplinary team
- Primary care physicians provide for patient's physical health care
- University affiliations/opportunities to work with forensic fellows and psychiatry residents
- On-site CME activities and paid CME leave time
- 35 hour work week
- Generous compensation for voluntary on-call available
- Private Practice Permitted
- 13 paid holidays
- Generous medical and dental benefits and retirement packages for full-time positions

Candidates must possess N.J. medical license

The Department of Health welcomes J1 Visa/Conrad 30 Program applicants. Additionally, the Department participates in a variety of State and federal workforce development and incentive programs ranging from, but not limited to the department's tuition reimbursement program and the Federal Student Loan Redemption Program. Additional information provided upon request.

Interested candidates should send a cover letter and detailed resume to:

Evan Feibusch, M.D. | Medical Director, DBHS
Evan.Feibusch@doh.nj.gov | 609.913.5316

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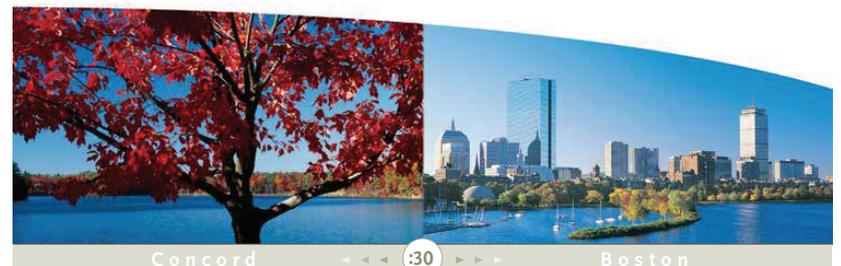


Hospital Locations:

- ★ Greystone Park Psychiatric Hospital (Morristown, NJ (Northern NJ))
- ★ Trenton Psychiatric Hospital (Trenton, NJ (Central NJ))
- ★ Ann Klein Forensic Center (Trenton, NJ (Central NJ))
- ★ Special Treatment Unit (Avenel, NJ (Northern NJ))
- ★ Ancora Psychiatric Hospital (Hammononton, NJ (Southern NJ))



Inpatient Psychiatry



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Exciting opportunity to join the psychiatry department at Emerson Hospital, a vibrant community hospital located in historic Concord, Massachusetts. We have full-time as well as moonlighting opportunities available. You will join a group of excellent psychiatrists, primary responsibilities include:

- Treatment of patients on our adult inpatient unit
- Consultation on psychiatrically ill patients on the medical units and collaboration with our medical colleagues
- Back-up for our Emergency Services
- Weekend, weeknight and holiday call in rotation
- Competitive salary and compensation package
- Additional income from moonlighting

For inquiries, please contact:

Diane Forte Willis
dfortewillis@emersonhosp.org
phone: 978-287-3002
fax: 978-287-3600

About Concord, MA and Emerson Hospital



Located in Concord, Massachusetts Emerson is a 179-bed community hospital with satellite facilities in Westford, Groton and Sudbury. The hospital provides advanced medical services to over 300,000 individuals in over 25 cities and towns.

Emerson has strategic alliances with Massachusetts General Hospital, Brigham and Women's and Tufts Medical Center.

Concord area is rich in history, recreation, education and the arts and is located 20 miles west of downtown Boston.



DEPARTMENT OF PSYCHIATRY

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)
- **Medical Director ED/Crisis:** Jersey Shore University Medical Center (Neptune, NJ)
- **Inpatient:** Raritan Bay Medical Center (Perth Amboy, NJ)
- **Outpatient:** Ocean Medical Center (Brick, NJ) and (Manahawkin, NJ)
- **Medical Director for Adult Inpatient Unit:** Riverview Medical Center (Red Bank, NJ)
- **Outpatient:** Southern Ocean Medical Center (Manahawkin, NJ)
- **Outpatient Child & Adolescent Psychiatrist:** Hackensack University Medical Center (Hackensack, NJ)
- **Geriatric Psychiatry:** Hackensack University Medical Center (Hackensack, NJ)
- **ED/Crisis Unit:** Jersey Shore University Medical Center (Neptune, NJ)
- **Telehealth Remote Psychiatrist FT/PT**

Renee.Theobald@hmhn.org
or call: 908 - 839 - 5693



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Northwell Health’s Behavioral Health Service Line strives to address the diverse mental health needs of the communities we serve by providing a continuum of accessible, high quality psychiatric and substance abuse services including emergency, crisis, inpatient, and outpatient programs for people of all ages. Northwell’s clinical programs are complemented by a robust education, training, and research enterprise, including the world-renowned Psychiatry Research Department at The Zucker Hillside Hospital, which has led cutting-edge investigations that have meaningfully influenced many lives.

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Cohen Children’s Medical Center
New Hyde Park, NY

CHILD AND ADOLESCENT PSYCHIATRIST, SCHOOL MENTAL HEALTH
Cohen Children’s Medical Center
New Hyde Park, NY

OUTPATIENT PSYCHIATRIST, PHELPS CONTINUING DAY TREATMENT PROGRAM
Phelps Memorial Hospital
Sleepy Hollow, NY

PHYSICIAN-IN-CHARGE, PERINATAL PSYCHIATRY
The Zucker Hillside Hospital
Glen Oaks, NY

ADULT OUTPATIENT PSYCHIATRIST
The Zucker Hillside Hospital
Glen Oaks, NY

***SOUTH OAKS HOSPITAL-AMITYVILLE, NY**

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- Evaluations/Admissions Psychiatrist
- Child and Adolescent Psychiatrist for Outpatient C&A clinic (COBS) position

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Lenox Health
Greenwich Village, NY

MEDICAL DIRECTOR, LBGTO TRANSGENDER MEDICINE
The Zucker Hillside Hospital
Glen Oaks, NY

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Long Island Jewish Medical Center
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Our Geriatric Psychiatry Fellowship is now accepting applications

Qualified candidates should forward their CV to Aderonke Adeyeye: OPR@northwell.edu



Psychiatrists: We're recruiting Medical Directors

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

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

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

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

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- **\$323,004 - \$383,916/year**
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 California Department of
State Hospitals

CALIFORNIA



Psychiatrist Position Excellent Opportunity in California

Imperial County Behavioral Health Services is currently recruiting for full-time or part-time psychiatrists. Imperial County, a rich farming area with a population of 180,000, is located 90 miles east of San Diego, 90 miles south of Palm Springs, 60 miles west of Yuma, Arizona, and just north of the cosmopolitan city of Mexicali, Mexico. San Diego State University maintains a satellite campus in Calexico, and there are several private and public universities located in Mexicali. Imperial County's location and diversity make it the perfect place for any professional.

The position pays a highly competitive salary, including health benefits for you and your family, requires no hospital work and minimal after-hours work, freeing you up for more leisurely activities. As a Psychiatrist with Imperial County Behavioral Health, you will be part of a multi-disciplinary treatment team that includes therapists, nurses and rehabilitation technicians that provide comprehensive support and resources to assist clients in achieving recovery.

J-1 and H1-B Applicants welcome. Our agency is experienced in successfully processing J-1 Waiver and H-1B Visa applicants.

Qualified candidates must have a CA medical license or ability to obtain. Send CV to Imperial County Behavioral Health Services, 202 North 8th Street, El Centro, CA 92243.

For additional information, please contact: Marcy Sesma (442) 265-1605
marcysesma@co.imperial.ca.us



Full-time psychiatrist for a large public health & hospital system in the Silicon Valley

\$275,080 - \$357,600 annually 36 days of annual leave Full benefits & retirement (Above annual salary includes additional pay for Board Certification and Acute Settings)

Santa Clara Valley Health and Hospital System, a public healthcare system in the heart of Silicon Valley, is seeking full-time BE/BC psychiatrists for a variety of clinical settings, including emergency psychiatric services, inpatient consultation

liaison services, jail custody health inpatient services, specialty mental health outpatient services and primary care behavioral health services.

As the largest public health care system in northern California, we offer comprehensive healthcare resources to a large and diverse patient population. Psychiatrists are part of a robust team of staff that work in

collaboration with other medical specialties and behavioral health clinicians to provide integrated health care to patients.

Psychiatrists are eligible for numerous benefits including 36 days of annual leave, 5 days of educational leave, 12 holidays, \$4500 educational funds, health benefits, life insurance and CalPERS retirement plan. No calls required.

In addition, part-time opportunities for BE/BC psychiatrists, PGY IIIs and IVs are available.

If you are interested in working in a dynamic and collegial work environment, please submit a CV and letter of interest to

MD.Recruitment@hhs.sccgov.org.

The County of Santa Clara is an Equal Opportunity.



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

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

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PSYCHIATRIC MEDICAL PRACTITIONERS, INC OUTPATIENT Full-time TELE-PSYCHIATRY POSITION

BE/BC ADULT PSYCHIATRIST licensed or willing to practice in CA, Practice from current State of Residence
Candidate has to be EHR and Computer proficient. You will be doing Psychiatric Evals & Med Mgt of SMI patients in County MH Clinics. There is no On-Call.

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Send CV to Garewalmd@gmail.com, or fax CV to (661) 368-0826



PORTERVILLE DEVELOPMENTAL CENTER
Has a Vacancy for:
Staff Psychiatrist
\$21,681 - \$26,736/month

Minimum Qualifications: Possession of the legal requirements for the practice of medicine in California as determined by the California Board of Medical Quality Assurance or the Board of Osteopathic Examiners. (Applicants who are in the process of securing approval of their qualifications by the Board of Medical Quality Assurance of the Board of Osteopathic Examiners will be admitted to the examination, but the Board to which

application is made must determine that all legal requirements have been met before candidates will be eligible for appointment.) and One year of experience in the practice of psychiatry or completion of one year of an approved residency in psychiatry.

Porterville Developmental Center (PDC) is located on about 670 acres in the foothills of the majestic Sierra Nevada Mountains in Porterville, California, an agricultural city in Tulare County. PDC is one of two State-operated facilities within the California Department of Developmental Services serving people with developmental disabilities. PDC provides 24-hour residential services for individuals 18 years or older who have serious medical and/or behavior problems for which appropriate services are not currently available through community resources. PDC is licensed by the California Department of Public Health to provide general acute medical services, skilled nursing services, and intermediate care services.

Majority of individuals served at PDC have an intellectual disability and many have severe chronic medical or behavioral problems. Others require services within a secure treatment program. These individuals are in the mild to moderate range of intellectual disability, have come in contact with the legal system, have been determined to be a danger to themselves or others and/or incompetent to stand trial, and have been determined by the court to meet the criteria requiring treatment in a secure area.

We offer excellent State Benefits - health, dental, vision, and retirement.

**Send California State Applications to:
Porterville Developmental Center
Attention: Recruitment and Examinations
P.O. Box 2000
Porterville, Ca. 93258**

For information call 559-782-2087 or go to the Calcareers Website at www.calcareers.ca.gov

MARYLAND



Psych Associates of Maryland is now Hiring

Behavioral Health Professionals Needed
Psych Associates of Maryland is expanding its outpatient group practice and is looking for board certified or eligible general psychiatrists, child, and adolescent psychiatrists to join the team.

Our practice is multidisciplinary and serves a patient population that carries commercial insurance or prefers to pay privately for their care. We treat our patients with compassion and respect. Our focus is on making it easier for providers to provide the quality of care in a relaxed environment and for patients to receive care in an environment of understanding.



Inpatient Child/Adolescent Psychiatrist Opportunities Cambridge Health Alliance

The NEW CHA Center of Excellence for Child & Adolescent Inpatient Mental Health Care at Somerville will provide a transformative continuum of patient- and family- centered care for diverse youth with mental health needs. Including specialized autism spectrum/ neurodevelopmental beds at our Somerville Campus. Cambridge Health Alliance is already one of the region's leading providers of behavioral and mental health care.

We are passionate about helping children and their families, join our expanding team and make a difference! CHA provides **Competitive Salaries starting at \$300,000 and Sign on Bonuses!**

- Provide clinical care to patients during periods of inpatient/partial hospitalization
- Develop and maintain comprehensive treatment plans
- Participate in teaching opportunities with psychiatry residents, fellows, and other mental health trainees
- Work in a collaborative practice environment with an innovative clinical model allowing our providers to focus on patient care and contribute to population health efforts
- Fully integrated electronic medical record (Epic) and robust interpreter service
- Academic appointments are available commensurate with criteria of Harvard Medical School
- **Candidates with special interest and training in Neurodevelopment encouraged to apply**

Qualified candidates will be BC/BE in psychiatry and share CHA's passion for providing the highest quality care to our underserved and diverse patient population. Please submit CV's through our secure website at www.CHAproviders.org, or by email to Melissa Kelley at ProviderRecruitment@challiance.org. The Department of Provider Recruitment may be reached by phone at (617) 665-3555 or by fax (617) 665-3553.

In keeping with federal, state and local laws, Cambridge Health Alliance (CHA) policy forbids employees and associates to discriminate against anyone based on race, religion, color, gender, age, marital status, national origin, sexual orientation, relationship identity or relationship structure, gender identity or expression, veteran status, disability or any other characteristic protected by law. We are committed to establishing and maintaining a workplace free of discrimination. We are fully committed to equal employment opportunity. We will not tolerate unlawful discrimination in the recruitment, hiring, termination, promotion, salary treatment or any other condition of employment or career development. Furthermore, we will not tolerate the use of discriminatory slurs, or other remarks, jokes or conduct, that in the judgment of CHA, encourage or permit an offensive or hostile work environment.

- Evaluation
- Medication management
- TMS Therapy
- Neuro psych testing
- Psychological testing
- Individual and group therapy
- We are also planning to expand upon clinical trials and studies, ketamine and suboxone infusions, and ABA
- J1 waivers
- Monday to Friday flexible schedules with no weekend patient care or administrative tasks
- Best in the industry and flexible compensation packages to attract the best talent

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NORTH CAROLINA



SEEKING PART TIME/ FULL TIME ADULT OR CHILD & ADOLESCENT PSYCHIATRIST (BE/BC) to join an established group practice in Cary, NC.

Out-patient only, fee-for-service, busy, no managed care, multidisciplinary group with child, adolescent, and adult psychiatrists and psychologists in a family oriented practice and community consistently rated as the top place to live in the country. Just minutes from RTP and 3 major universities. Flexibility in job, excellent collections and benefits.

Email CV to Office Manager, Jyoti Gawdi at jgawdi@fppa.com. Website: www.fppa.com

OREGON



Samaritan Health Services

This full-time position offers teaching and patient care in an outpatient setting. You will be providing patient care 80 percent of the time and spend remaining time supervising residents or participating in academic duties.

Job Requirements

- Board Certified or Board Eligible in Psychiatry
- Current Oregon Licensure or eligibility
- Knowledge of working with patients who have chronic health conditions
- Experience in psychodynamic

psychotherapy preferred

Benefits include:

- Competitive compensation
- Medical malpractice paid
- Continuing medical education
- Relocation allowance
- Starting bonus

Psychiatrists

NYC
HEALTH+
HOSPITALS

North
Central
Bronx

At **New York City Health + Hospitals/North Central Bronx** our goal is to make an impact on the communities we serve, each and every day! We are a modern, state-of-the-art community hospital located in an attractive and safe residential Bronx neighborhood just 20 minutes north of Manhattan. The Department of Psychiatry has 70 Adult and Geriatric Acute Inpatient Beds, a Partial Hospital Program, Psychiatric Emergency Service, Consultation-Liaison Service, an Adult Ambulatory Practice, and a community-based Assertive Community Treatment Program.

Opportunities are currently available for the following:

- Attending Psychiatrist - Inpatient Psychiatry Service
- Director of Psychiatry - Emergency Services
- Attending Psychiatrist - Psychiatric Emergency Service
- Attending Psychiatrist - Partial Hospital Program
- Attending Psychiatrist - Inpatient Geriatric Psychiatry Service

NYC
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HOSPITALS

Jacobi

The **Department of Psychiatry at New York City Health + Hospitals/Jacobi** Hospitals/Jacobi offers the opportunity to make a real impact! With 89 Adult, Acute Inpatient beds, a Comprehensive Psychiatric Emergency Program (CPEP), a Consultation-Liaison Service, Adult Ambulatory Practice, Intensive Outpatient Program, and a Community-Based Assertive Community

Treatment Program, we are well positioned to perform life sustaining work. Join our modern, state-of-the-art facility that offers a Level 1 Trauma Center, and located in an attractive and safe residential Bronx neighborhood, just 20 minutes from Manhattan.

Opportunities are currently available for the following:

- Attending Psychiatrist - Inpatient Psychiatry Service
- Attending Psychiatrist - CPEP

Both hospitals are part of the North Bronx Healthcare Network, are teaching sites and academic affiliates of the Albert Einstein College of Medicine, offering a full continuum of acute care inpatient and outpatient services within diverse Medical and Surgical specialties, including Psychiatry. Our departments employ evidence-based best practices in providing the highest level of quality care to its patients, utilizing a patient-centered approach that is respectful of their individuality, culture, and community.

Moonlighting opportunities also available! An academic appointment at Albert Einstein College of Medicine is offered!

We offer a generous compensation package, and unparalleled health benefits, opportunities for advancement, retirement plan, malpractice, Sponsorship for H1 & J1 Visas, and much more!

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Discovering Psychiatry Throughout the 5 Boroughs.
<https://www.psychiatrictimes.com/view/discovering-psychiatry>

Physician Affiliate Group of New York [PAGNY] provides services to NYC Health + Hospitals Corporation (H + H), the largest public healthcare system in the United States. EOE M/F/D/V

For more information, or to apply please visit www.samhealth.org/DocJobs or contact Valerie Fulleton at 541-768-4766.

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@AmCareServices.com

RHODE ISLAND



Lifespan

In & Outpatient Psychiatry - Brown University Academic Appointment

We have an opportunity for a board certified or eligible psychiatrist with interest in working in both an in & outpatient setting. This is a great opportunity to work with a variety of patients while positively impacting your income. Based in Providence or Newport, our programs encompass a comprehensive view of mental health that includes and integrates the biological, psychological and social dimensions of care.

Additional details

- Average 6 inpatients per morning, with outpatient schedule in the afternoon
- Patients 18 and over
- Mix of diagnoses: psychotic disorders, mood disorders, PTSD, personality disorders, co-occurring substance use disorders
- Inpatient behavioral health team includes nurses, psych techs, social workers, recreation therapist
- Call schedule varies by location and is shared equitably
- Potential for a Brown Academic appointment
- J1 and H1b visa friendly

For additional information please forward CV to Hillary Woodyatt, hwoodyatt@lifespan.org

SOUTH CAROLINA

PRISMA HEALTH.

Inspire health. Serve with compassion. Be the difference.

Child & Adolescent Psychiatrist Greenville, SC

Prisma Health, the largest healthcare provider in South Carolina, currently seeks BC/BE Child & Adolescent Psychiatrists to join our growing psychiatry department. The department is expanding our clinical, education, and research missions and is seeking candidates in all specialties.

Successful candidates will have the opportunity to work within our specialty outpatient clinics and/or programs, and work across disciplines with other departments. Ideal candidates will have an interest in teaching and be eligible for faculty appointment at University of South Carolina School of Medicine Greenville, located on Prisma Health's Greenville Memorial Medical Campus.

Details Include:

- Candidate must be fellowship-trained and BE/BC in child and adolescent psychiatry
- Experience in an outpatient mental health setting, including telepsychiatry services
- Monday - Friday Outpatient with 1:7 weekend inpatient coverage
- Academic faculty position working with fellows, residents and medical students
- Competitive compensation
- Rich benefits package including relocation, malpractice, health and dental insurance
- CME allowance

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

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@prismahealth.org,

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

WANT TO
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INGREZZA® (valbenazine) capsules

for oral use

Brief Summary: for full Prescribing Information and Patient Information, refer to package insert.

INDICATION AND USAGE

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 VMAT2 inhibitors. In the 3 placebo-controlled clinical studies in patients with tardive dyskinesia, the incidence of parkinson-like adverse events was 3% of patients treated with INGREZZA and <1% of placebo-treated patients. Postmarketing safety reports have described parkinson-like symptoms, some of which were severe and required hospitalization. In most cases, severe parkinsonism occurred within the first 2 weeks after starting or increasing the dose of INGREZZA. Associated symptoms have included falls, gait disturbances, tremor, drooling, and hypokinesia. In cases in which follow-up clinical information was available, parkinson-like symptoms were reported to resolve following discontinuation of INGREZZA therapy. Reduce the dose or discontinue INGREZZA treatment in patients who develop clinically significant parkinson-like signs or symptoms.

ADVERSE REACTIONS

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

- 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/schizoaffective disorder (72%). The mean age was 56 years. Patients were 57% Caucasian, 39% African-American, and 4% other. With respect to ethnicity, 28% were Hispanic or Latino. All subjects continued previous stable regimens of antipsychotics; 85% and 27% of subjects, respectively, were taking atypical and typical antipsychotic medications at study entry.

Adverse Reactions Leading to Discontinuation of Treatment

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

Common Adverse Reactions

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

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

Adverse Reaction ¹	INGREZZA (n=262) (%)	Placebo (n=183) (%)
General Disorders		
Somnolence (somnolence, fatigue, sedation)	10.9%	4.2%
Nervous System Disorders		
Anticholinergic effects (dry mouth, constipation, disturbance in attention, vision blurred, urinary retention)	5.4%	4.9%
Balance disorders/fall (fall, gait disturbance, dizziness, balance disorder)	4.1%	2.2%
Headache	3.4%	2.7%
Akathisia (akathisia, restlessness)	2.7%	0.5%
Gastrointestinal Disorders		
Vomiting	2.6%	0.6%
Nausea	2.3%	2.1%
Musculoskeletal Disorders		
Arthralgia	2.3%	0.5%

¹ 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: drooling, 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 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

Drugs Having Clinically Important Interactions with INGREZZA

Table 2: Clinically Significant Drug Interactions with INGREZZA

Monoamine Oxidase Inhibitors (MAOIs)	
<i>Clinical Implication:</i>	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.
<i>Prevention or Management:</i>	Avoid concomitant use of INGREZZA with MAOIs.
<i>Examples:</i>	isocarboxazid, phenelzine, selegiline
Strong CYP3A4 Inhibitors	
<i>Clinical Implication:</i>	Concomitant use of INGREZZA with strong CYP3A4 inhibitors increased the exposure (C _{max} 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.
<i>Prevention or Management:</i>	Reduce INGREZZA dose when INGREZZA is coadministered with a strong CYP3A4 inhibitor.
<i>Examples:</i>	itraconazole, ketoconazole, clarithromycin
Strong CYP2D6 Inhibitors	
<i>Clinical Implication:</i>	Concomitant use of INGREZZA with strong CYP2D6 inhibitors increased the exposure (C _{max} and AUC) to valbenazine's active metabolite compared with the use of INGREZZA alone. Increased exposure of active metabolite may increase the risk of exposure-related adverse reactions.
<i>Prevention or Management:</i>	Reduce INGREZZA dose when INGREZZA is coadministered with a strong CYP2D6 inhibitor.
<i>Examples:</i>	paroxetine, fluoxetine, quinidine
Strong CYP3A4 Inducers	
<i>Clinical Implication:</i>	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.
<i>Prevention or Management:</i>	Concomitant use of strong CYP3A4 inducers with INGREZZA is not recommended.
<i>Examples:</i>	rifampin, carbamazepine, phenytoin, St. John's wort ¹
Digoxin	
<i>Clinical Implication:</i>	Concomitant use of INGREZZA with digoxin increased digoxin levels because of inhibition of intestinal P-glycoprotein (P-gp).
<i>Prevention or Management:</i>	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.

¹ The induction potency of St. John's wort may vary widely based on preparation.

Drugs Having No Clinically Important Interactions with INGREZZA

Dosage adjustment for INGREZZA is not necessary when used in combination with substrates of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1, 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 Overdosage

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.poison.org).

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



Distributed by:
Neurocrine Biosciences, Inc.
San Diego, CA 92130

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CP-VBZ-US-0203v5 05/2020

ONCE-DAILY
INGREZZA[®]
 (valbenazine) capsules

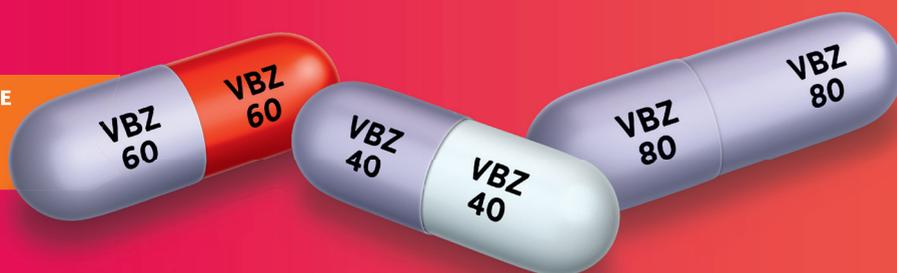
#1

**MOST PRESCRIBED TREATMENT
 FOR TARDIVE DYSKINESIA¹**

THE SIMPLE CHOICE

FOR YOUR PATIENTS WITH TARDIVE DYSKINESIA (TD)

NOW AVAILABLE
 60 mg
 Capsule



Not actual size.

ONLY INGREZZA OFFERS
 ALL THE EASE OF²:



One capsule, once daily

3

Effective dosing options



No titration required



Taken any time of day



Taken with or without food

Give your patients all the ease of INGREZZA. See more at [INGREZZAHCP.com/Dosing](https://www.ingrezzahcp.com/dosing)

Important Information

INDICATION & USAGE

INGREZZA[®] (valbenazine) capsules is indicated for the treatment of adults with tardive dyskinesia.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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Somnolence

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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 ($\geq 5\%$ and twice the rate of placebo) is somnolence. Other adverse reactions ($\geq 2\%$ 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](https://www.neurocrine.com/INGREZZAPI) for full Prescribing Information.

REFERENCES: 1. Data on file. Neurocrine Biosciences, Inc. 2. INGREZZA [package insert]. San Diego, CA: Neurocrine Biosciences, Inc.

