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COMMENTARY

Federal Court Gives Green Light to

DENY COVERAGE

Thomas Insel, MD

Nearly every psychiatric clinician I know has experienced it: Their patient's health plan determines—with little justification—that the needed treatment is "not medically necessary." The clinician is then forced to spend valuable time fighting for coverage of the treatment that is validated by accepted clinical standards of care. Meanwhile, families confront their options: spending life savings, taking on burdensome debt, or going without treatment. *Continued on page 9*

PSYCHIATRY & SOCIETY

The Online, At-Home Ketamine Experience: A Clinician's Dilemma

Michael D. Banov, MD; Rachel E. Landrum, MA

CASE VIGNETTE 1 "Mr Brad," a 46-year-old, employed man, is seen in our clinic for medication management of chronic unipolar depression, generalized anxiety, and attention-deficit/hyperactivity disorder. At his most recent visit, he proactively shared that he was in the process of starting at-home ketamine through an online health care provider. He has tried various antidepressant and antianxiety medications, Continued on page 11

Auvelity™

(dextromethorphan HBr and bupropion HCl)
extended-release tablets 45mg/105mg

NOW APPROVED

Auvelity is the first and only oral NMDA receptor antagonist approved for the treatment of major depressive disorder in adults.[1-3]

Auvelity is the first and only rapid-acting oral treatment approved with labeling of statistically significant improvement in depressive symptoms compared to placebo starting at 1 week.[1*]

Auvelity uses a new approach to treat major depressive disorder that is different from other oral antidepressants approved in more than 60 years.[1-3†]

INDICATION

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

IMPORTANT SAFETY INFORMATION

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

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

CONTRAINDICATIONS

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

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

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

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

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

WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

FDA Breakthrough Therapy Designation

Ready for a new way to treat MDD?

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

*As measured by change from baseline in MADRS total score.
†The mechanism of action of Auvelity in the treatment of MDD is unclear.
MADRS=Montgomery-Åsberg Depression Rating Scale; NMDA=N-methyl-D-aspartate

IMPORTANT SAFETY INFORMATION (CONT'D)

Dizziness: Auvelity may cause dizziness. Precautions to reduce the risk of falls should be taken, particularly for patients with motor impairment affecting gait or a history of falls. Caution patients about operating hazardous machinery, including motor vehicles, until they are reasonably certain that Auvelity therapy does not affect them adversely.

Serotonin Syndrome: Auvelity contains dextromethorphan. Concomitant use with selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants increases the risk of serotonin syndrome, a potentially life-threatening condition. Prior to initiating therapy with Auvelity, screen patients for use of other dextromethorphan-containing products. If concomitant use of Auvelity with other serotonergic drugs is clinically warranted, inform patients of the increased risk for serotonin syndrome, and monitor for symptoms. Discontinue Auvelity and/or concomitant serotonergic drug(s) immediately if symptoms of serotonin syndrome occur and initiate supportive symptomatic treatment.

Embryo-fetal Toxicity: Based on animal studies, Auvelity may cause fetal harm when administered during pregnancy. Discontinue treatment in pregnant females and advise the patient about the potential risk to a fetus. Use alternative treatment for females who are planning to become pregnant.

DRUG INTERACTIONS

Strong Inhibitors of CYP2D6: Concomitant use with Auvelity increases plasma concentrations of dextromethorphan. Dosage adjustment is necessary. Monitor patients for adverse reactions potentially attributable to dextromethorphan, such as somnolence and dizziness.

Strong CYP2B6 Inducers: Concomitant use with Auvelity decreases plasma concentrations of dextromethorphan and bupropion and may decrease efficacy of Auvelity. Avoid co-administration of Auvelity.

CYP2D6 Substrates: Concomitant use with Auvelity can increase the exposures of drugs that are substrates of CYP2D6. It may be necessary to decrease the dose of CYP2D6 substrates, particularly for drugs with a narrow therapeutic index.

Digoxin: Concomitant use with Auvelity may decrease plasma digoxin levels. Monitor plasma digoxin levels in patients treated concomitantly with Auvelity.

Drugs that Lower Seizure Threshold: Concomitant use with Auvelity may increase risk of seizure. Use Auvelity with caution. Discontinue Auvelity and do not restart treatment if the patient experiences a seizure.

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

USE IN SPECIFIC POPULATIONS

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

Renal Impairment: Dosage adjustment is recommended in patients with moderate renal impairment (eGFR 30 to 59 mL/minute/1.73 m^2). Auvelity is not recommended in patients with severe renal impairment (eGFR 15 to 29 mL/minute/1.73 m^2).

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

ADVERSE REACTIONS

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

AUV HCP ISI 08/2022

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

References: 1. Auvelity [Prescribing Information]. Axsome Therapeutics, Inc.: New York, NY. **2.** FDA Depression Medicines. https://www.fda.gov/media/132665/download. Accessed March 21, 2022. **3.** Thomas D, and Wessel C. The state of innovation in highly prevalent chronic diseases volume I: Depression therapeutics. December 2017. https://www.bio.org/sites/default/files/legacy/bioorg/docs/BIO_HPCD_Series-Depression_2018-01-03.pdf. Accessed March 21, 2022.

axsome®

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

Brief Summary of Prescribing Information

BEFORE PRESCRIBING AUVELITY, PLEASE SEE FULL PRESCRIBING INFORMATION, INCLUDING BOXED WARNING.

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

See full prescribing information for complete boxed warning.

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

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

AUVELITY is contraindicated in patients:

- with a seizure disorder
- with a current or prior diagnosis of bulimia or anorexia nervosa as a higher incidence of seizures was observed in such patients treated with the immediate release formulation of bupropion
- undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs
- taking, or within 14 days of stopping, MAOIs due to the risk of serious and possibly fatal drug interactions, including hypertensive crisis and serotonin syndrome. Starting AUVELITY in a patient treated with reversible MAOIs such as linezolid or intravenous methylene blue is contraindicated.
- with known hypersensitivity to bupropion, dextromethorphan, or other components of AUVELITY. Anaphylactoid / anaphylactic reactions and Stevens-Johnson syndrome have been reported with bupropion. Arthralgia, myalgia, fever with rash, and other serum sickness-like symptoms suggestive of delayed hypersensitivity have also been reported with bupropion.

WARNINGS AND PRECAUTIONS

Suicidal Thoughts and Behaviors in Adolescents and Young Adults

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

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

Age Range	Drug-Placebo Difference in Number of Patients of Suicidal Thoughts or Behaviors per 1000 Patients Treated
	Increases Compared to Placebo
<18 years old	14 additional patients
18-24 years old	5 additional patients
	Decreases Compared to Placebo
25-64 years old	1 fewer patient
≥65 years old	6 fewer patients

*AUVELITY is not approved for use in pediatric patients.

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

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

Seizure

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

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

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

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

Increased Blood Pressure and Hypertension

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

Activation of Mania/Hypomania

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

Psychosis and Other Neuropsychiatric Reactions

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

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

Angle-Closure Glaucoma

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

Dizziness

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

Serotonin Syndrome

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

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

Embryo-fetal Toxicity

Based on animal studies, AUVELITY may cause fetal harm when administered during pregnancy. In developmental toxicity studies in rats and rabbits, when a combination of dextromethorphan/quinidine was given to pregnant animals, fetal malformations (rabbits) and embryolethality were demonstrated in offspring. Neurotoxicity findings were observed in juvenile rats treated with a combination of dextromethorphan/quinidine on postnatal day (PND) 7, which corresponds to the third trimester of gestation through the first few months of life and may extend through the first three years of life in humans. The separate effect of dextromethorphan on developmental toxicity at the recommended clinical dose is unclear. Discontinue treatment in pregnant females and advise the patient about the potential risk to a fetus. Use alternative treatment for females who are planning to become pregnant.

ADVERSE REACTIONS

Clinical Trials Experience

AUVELITY was evaluated for safety in a total of 1114 patients with MDD or another indication from four studies (two 6-week studies in MDD, one 6-week study in another indication, and one long-term study in MDD and another indication). One 6-week study in MDD employed placebo as a control arm. Two 6-week studies, one in MDD and one in another indication, employed bupropion as a control arm. In the patients treated with AUVELITY in the long-term study (n=876), 597 received at least 6 months of treatment, and 110 received at least 12 months of treatment. The data below are based on the 6-week, placebo-controlled study in which either AUVELITY (n=162) or placebo (n=164) was administered twice daily to patients with MDD (Study 1).

Adverse Reactions Leading to Discontinuation
In the 6-week placebo-controlled study, 4% of patients treated with AUVELITY and 0% of placebo-treated patients discontinued participation due to adverse reactions. The adverse reaction that led to study discontinuation in ≥1% of patients treated with AUVELITY was anxiety (2%).

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

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

Adverse Reaction	AUVELITY (N=162) %	Placebo (N=164) %
Dizziness	16	6
Nausea	13	9
Headache	8	4
Diarrhea	7	3
Somnolence	7	3
Dry mouth	6	2
Sexual dysfunction[a]	6	0
Hyperhidrosis	5	0
Anxiety	4	1
Constipation	4	2
Decreased appetite	4	1
Insomnia	4	2
Arthralgia	3	0
Fatigue[b]	3	2
Paraesthesia[c]	3	0
Vision blurred	3	0

[a]Sexual dysfunction includes orgasm abnormal, erectile dysfunction, libido decreased, anorgasmia
[b]Fatigue includes fatigue, lethargy
[c]Paraesthesia includes paraesthesia, hypoaesthesia

DRUG INTERACTIONS

Table 3: Clinically Important Drug Interactions with AUVELITY

Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact	The concomitant use of AUVELITY with MAOIs increases the risk of hypertensive crisis and serotonin syndrome.
Intervention	AUVELITY is contraindicated in patients taking MAOIs (including MAOIs such as linezolid or intravenous methylene blue) or in patients who have taken MAOIs within the preceding 14 days. Allow at least 14 days after stopping AUVELITY before starting an MAOI.
Serotonergic Drugs	
Clinical Impact	Concomitant use of AUVELITY with other serotonergic drugs increases the risk of serotonin syndrome.
Intervention	Monitor for symptoms of serotonin syndrome when AUVELITY is used concomitantly with other drugs that may affect the serotonergic neurotransmitter systems. If serotonin syndrome occurs, consider discontinuation of AUVELITY and/or concomitant serotonergic drugs.
Drugs that Lower Seizure Threshold	
Clinical Impact	AUVELITY contains bupropion which can cause seizure. Co-administration with other drugs that lower seizure threshold may increase risk of seizure.
Intervention	Use caution when administering AUVELITY concomitantly with drugs that lower the seizure threshold. Discontinue AUVELITY and do not restart treatment if the patient experiences a seizure.
Strong Inhibitors of CYP2D6	
Clinical Impact	Concomitant use of AUVELITY with strong CYP2D6 inhibitors increases plasma concentrations of dextromethorphan.
Intervention	Dosage adjustment is necessary when AUVELITY is coadministered with strong inhibitors of CYP2D6. Monitor patients for adverse reactions potentially attributable to dextromethorphan, such as somnolence and dizziness.
Strong Inducers of CYP2B6	
Clinical Impact	Concomitant use of AUVELITY with strong CYP2B6 inducers decreases plasma concentrations of dextromethorphan and bupropion and may decrease efficacy of AUVELITY.
Intervention	Avoid co-administration of AUVELITY with strong inducers of CYP2B6. Consider alternatives to strong CYP2B6 inducers if needed.
Drugs Metabolized by CYP2D6	
Clinical Impact	*CYP2D6 Substrates* Coadministration of AUVELITY with drugs that are metabolized by CYP2D6 can increase the exposures of drugs that are substrates of CYP2D6. *Drugs that Require Metabolic Activation by CYP2D6* Drugs that require metabolic activation by CYP2D6 to be effective could have reduced efficacy when administered concomitantly with AUVELITY.
Intervention	*CYP2D6 Substrates* When used concomitantly with AUVELITY, it may be necessary to decrease the dose of CYP2D6 substrates, particularly for drugs with a narrow therapeutic index. *Drugs that Require Metabolic Activation by CYP2D6* Patients treated concomitantly with AUVELITY may require increased doses of drugs that require activation by CYP2D6 to be effective.
Digoxin	
Clinical Impact	Coadministration of AUVELITY with digoxin may decrease plasma digoxin levels.
Intervention	Monitor plasma digoxin levels in patients treated concomitantly with AUVELITY and digoxin.
Dopaminergic Drugs	
Clinical Impact	CNS toxicity was reported when bupropion was co-administered with levodopa or amantadine. Adverse reactions have included restlessness, agitation, tremor, ataxia, gait disturbance, vertigo, and dizziness.
Intervention	Use caution when administering AUVELITY concomitantly with dopaminergic drugs.
Alcohol	
Clinical Impact	AUVELITY contains bupropion which can increase adverse neuropsychiatric events or reduce alcohol tolerance.
Intervention	The consumption of alcohol should be minimized or avoided during treatment with AUVELITY.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antidepressants, including AUVELITY, during pregnancy. Healthcare providers are encouraged to register patients by contacting the National Pregnancy Registry for Antidepressants at 1-866-961-2388 or online at: https://womensmentalhealth.org/research/pregnancyregistry/antidepressants/

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

Clinical Considerations
Disease-Associated Maternal and/or Embryo/Fetal Risk
Women who discontinued antidepressants during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressants. Consider the risks to the mother of untreated depression and potential effects on the fetus when discontinuing or changing treatment with antidepressant medications during pregnancy and postpartum.

Lactation

Risk Summary

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

Renal Impairment

Dosage adjustment of AUVELITY is recommended in patients with moderate renal impairment (eGFR 30 to 59 mL/minute/1.73 m^2). The pharmacokinetics of AUVELITY have not been evaluated in patients with severe renal impairment. AUVELITY is not recommended in patients with severe renal impairment (eGFR 15 to 29 mL/minute/1.73 m^2).

Hepatic Impairment

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

CYP2D6 Poor Metabolizers

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

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In This Issue

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Publisher's Note

Navigating Rock-and-a-Hard-Place Situations

Challenges: They often drive us to learn, to grow, to do better. These rock-and-a-hard-place situations seem to be cropping up more and more every day. For example, what happens when you spend more time fighting with insurance companies than providing critical care for your patients? Or when you must manage a situation in which a patient is separately prescribed a substance via an online-only source that could interfere with the medications you prescribe? These pertinent, difficult questions will steer the future directions of psychiatry and medicine in general. In this month's cover stories, we explore these challenges to help you make informed, smart decisions in your own practice.

Speaking of common challenges, how can we best approach COVID-19 and mental health? Although the pandemic is far from over, we must learn to navigate what will be a post–COVID-19 world. According to James Lake, MD, in this month's continuing medical education article, complementary and alternative medicine interventions can enhance resilience and help address mental health problems due to the pandemic.

As we confront these challenges head-on, we must also remain mindful of what can provide much-needed downtime. What hobbies, activities, and interests soothe you when work is done? For regular contributor Mark L. Ruffalo, MSW, DPsa, it is Thoroughbred horse racing, and he shares his thoughts in a recent Medical World News® video (see: medicalworldnews.com/view/after-hours-horseman). Now more than ever, we cannot let challenges take us away from doing what we love.

At *Psychiatric Times*™, we challenge ourselves to provide the best pearls for you, cover to cover. ■

Mike Hennessy Jr
President and CEO, MJH Life Sciences®

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From the Editor

Virtually Malpractice

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

As our society has been slowly returning to our pre-COVID-19 structure, unforeseen dangerous residues from the necessary rapid adoption of telehealth have emerged that demand our attention and reconstruction. One of these is related to the 2021 decision by the Drug Enforcement Administration (DEA) to temporarily allow dispensing of controlled substances (Schedule 2 through Schedule 5) without the prescriber seeing the patient in person, which remains in effect.

A recent article in *The Wall Street Journal* chronicled the flagrant abuses and dangers in the subsequent prescribing of psychostimulants for presumed attention-deficit/hyperactivity disorder (ADHD) through a virtual platform, during which the psychostimulant prescriber never met with the patient in person for an initial evaluation or subsequent refills.[1]

This month's article by Michael D. Banov, MD, and Rachel E. Landrum, MA, provides a disturbing narrative of another unfortunate dangerous residue that is aggressively expanding via venture capitalists and opportunists in the United States due to this loosened DEA restriction: the growing enterprise of at-home virtual ketamine treatment. Both ketamine and esketamine are Schedule 3 drugs, and ketamine has a history of diversion, abuse, and dependence. On the street, ketamine is called Special K.

I was unaware of the rapidly growing at-home ketamine virtual treatment business until I read this article and subsequently researched the current state of this dangerous model of providing access to ketamine without the required medical oversight and monitoring necessary for accurate patient selection and safety. To my astonishment, the *Journal of Affective Disorders* just published an article online,[2] which appears in their October issue, detailing a large prospective open-label study of at-home, sublingual ketamine telehealth for moderate to severe anxiety and depression, stating in the title that it is "safe and effective." Notably, there is no placebo control group.

In my opinion, the publication of this article in this well-respected journal is irresponsible and dangerous. It gives credibility to a virtual

practice that falls far below the standard of care for the treatment of severe depression and also makes claims about safety and efficacy in anxiety. The scales used are the 9-item Patient Health Questionnaire and the 7-item Generalized Anxiety Disorder questionnaire, neither of which would be acceptable end points to assess symptom improvement in clinical trials. Additionally, this study uses "certified behavioral coaches" called *guides* whose clinical credentials are unclear. However, the Intervention section of the paper states that "guides are not licensed professionals and do not provide psychotherapy." The sublingual ketamine is mailed to the participants.

In the Methods section, the authors state "the [Mindbloom] platform is accessible through internet search or external physician/provider referral." However, I could not find a breakdown of the number of individuals who were referred versus the number who were self-selected by looking for a website to receive at-home ketamine. Most concerning is the way "side effects and adverse events were assessed through a single-item self-report measure administered after session 2 and again after session 4 that said, 'Have you noticed any issues with your physical or mental health since beginning treatment?' "

To provide context, ketamine was approved by the US Food and Drug Administration (FDA) in 1970 as a dissociative anesthetic, and its current FDA-approved indications are limited to general anesthesia and moderate to severe chronic pain. An iconic publication by Berman et al[3] demonstrated rapid antidepressant activity when intravenous ketamine was infused into patients with severe depression. Over the past 22 years, ketamine has been used off-label for the treatment of severe depression in various clinical settings and formulations (intravenous, intramuscular, intranasal, sublingual, and oral). In 2019, esketamine was approved by the FDA as an intranasal spray to be used in conjunction with a traditional antidepressant for treatment-resistant depression (TRD).

When ketamine is synthesized, it exists as a 50/50 racemic mixture of its 2 mirror-image components: arketamine and esketamine. Both of these racemates have demonstrated antidepressant activity, but, as of today, only esketamine is FDA-approved for TRD. Although head-to-head studies have not been conducted, clinical experience strongly suggests both ketamine and esketamine are effective in some patients with TRD. Of significance, none of these 3 molecules have established clinical efficacy for anxiety disorders, posttraumatic stress disorders, or other psychiatric disorders.

Additionally, due to the clear and well-documented risks of ketamine abuse, misuse, diversion, dependance, teratogenicity, risk of severe hypertension, common adverse effects of dissociation and sedation, and association with interstitial cystitis and cognitive impairment with long-term daily abuse, the FDA approved esketamine for TRD with a mandatory risk evaluation and mitigation strategies (REMS) protocol. There are approximately 60 medications (including clozapine and isotretinoin) for which the FDA requires REMS protocols. The REMS for esketamine requires certification by the clinic/administering prescriber and the dispensing pharmacy, and patient's informed consent. A REMS treatment form must be filled out and submitted after each dose of esketamine for the duration of treatment.

Patients receiving esketamine are required to have their blood pressure monitored pre-dose, and then 40 minutes and 2 hours after administration. They must remain in the treatment facility for monitoring by a health care professional for a minimum of 2 hours, the time period in which the common adverse effects of dissociation and sedation occur and will likely resolve. Patients agree that they will not drive themselves home or engage in any complex activity until after a good night's sleep.

The highly structured REMS protocol is required at the administration of each dose to minimize the possible harm to the patient based on more than 50 years of clinical experience with ketamine, which is 50% esketamine.

Keep these facts in mind as you review the **Table**, which I assembled by searching "at home ketamine" via Google. As clinicians who took an oath to "do no harm," we must educate the public about the dangers and non–standard of care of the growing practice of at-home ketamine.

Dr Miller would like to disclose that he is a member of the Speakers' Bureau for Janssen.

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TABLE. At-Home Ketamine Virtual Treatment Websites

Websites	Quotes From Website
www.mindbloom.com	"Clinicians on Mindbloom's platform may prescribe guided ketamine therapy for indications of depression or anxiety. Ketamine is a prescription medication that doctors can prescribe off-label to treat depression, anxiety, chronic pain, PTSD, OCD, and other mental health-related conditions."
nue.life	"Ketamine has full FDA approval and is used in hospitals every day as an anesthetic. Multiple clinical trials have shown ketamine's profound ability to treat depression, anxiety, bipolar illness, and PTSD. It's shorter-acting and more predictable than other psychedelics."
www.fieldtriphealth.com/ketamine-assisted-therapy	"Ketamine-assisted psychotherapy (KAP) is powerful but gentle. Unlike antidepressants which help manage symptoms, KAP helps to get to the root of the problem so you can heal. Ketamine opens the door to psychedelic exploration, allowing you to objectively revisit past events, life experiences, and traumas. When paired with the structure and support of talk therapy, you're able to process and understand these moments so that you can let go of some of the emotional attachments that you might be stuck on."
myketaminehome.com	"My Ketamine Home provides an alternative to expensive IV ketamine infusion therapy with our at-home oral program. Effective for managing depression, anxiety, bipolar, and post-traumatic stress disorder."
www.withpeak.com	"From regular check-ins to guided integration circles to full-service prescription management and more, Peak provides everything you need to make the most of ketamine therapy and find true peace of mind from the comfort of home."

From the Cover

Denying coverage

With more than 7.1 million American adults not receiving the mental health treatment they need because of cost,[1] ensuring health plans cover the services patients need is essential to maintaining and increasing access to care.

At the root of this issue is who makes the determinations about whether treatment is needed— and what standards should be and must be followed.

The Mental Health Parity and Addiction Equity Act of 2008 established the principle of parity for mental and physical health coverage. Although we have made progress, a significant barrier to achieving parity is insurers' frequent arbitrary determinations that needed care is not medically necessary.

Yet there has been hope in tackling this issue successfully. In 2019, a federal district court in San Francisco detailed in a more than 100-page ruling how United Behavioral Health (UBH), the nation's largest insurer of mental health care, used internally developed medical necessity criteria that were inconsistent with generally accepted standards of care to deny mental health and addiction coverage.[2] In so doing, the court ruled that UBH had violated its fiduciary duty to plan members under the federal Employee Retirement Income Security Act (ERISA).

After hearing expert clinical testimony, the court described the 8 generally accepted standards of mental health and substance use disorder care. These standards are listed in the **Table**.

The court then found that UBH's medical necessity criteria were inconsistent with each of these standards, resulting in inappropriate coverage denials for more than 50,000 patients.[2] Half of those patients were children or adolescents, and the son of 1 of the named plaintiffs died after receiving a denial of coverage.

According to the court, there was clear evidence that UBH used medical necessity determinations to limit the duration of coverage in an arbitrary manner and push patients into inappropriate lower (cheaper) levels of care.[2] UBH's process for developing medical necessity criteria were, the court determined, "infected" by its financial interests.

Importantly, all the experts at trial—including UBH's own witnesses—agreed that criteria to determine the appropriate level of care that are consistent with generally accepted standards of care already exist.[2] These criteria come from nonprofit clinical specialty associations, including the American Society of Addiction Medicine (ASAM), the American Academy of Clinical Psychiatrists, and the American Academy of Child and Adolescent Psychiatry. These associations' criteria provide holistic assessments of patients' needs and put patients' interests first.

TABLE. The 8 Generally Accepted Standards of Mental Health and Substance Use Disorder Care

1. Effective treatment requires treatment of the patient's underlying condition, not just alleviation of the patient's current symptoms.
2. Effective treatment requires treatment of comorbidities in a coordinated manner that considers their interactions when determining the appropriate level of care.
3. Patients should receive treatment at the least intensive and restrictive level of care that is safe and just as effective as a higher level of care.
4. When there is ambiguity as to the appropriate level of care, the clinician should err on the side of caution by placing the patient in the higher level of care.
5. Effective treatment includes services needed to maintain proper functioning or prevent deterioration.
6. The appropriate duration of treatment is based on the patient's individual needs, not on a specific limit on the duration of treatment.
7. The unique needs of children and adolescents must be taken into account.
8. The determination of the appropriate level of care should be made on a multidimensional assessment that takes into account a variety of information about the patient.

In fact, UBH's own internal clinicians believed that the ASAM criteria were most appropriate for substance use disorder determinations and recommended that UBH switch. This recommendation was vetoed, however, by UBH's finance department because of uncertainty of the financial impact of the switch.[2]

To fix the violations it found, the court ordered UBH to reprocess denials that were based on its own flawed criteria by using the nonprofit clinical professional associations' criteria and to use these criteria for mental health and substance use medical necessity determinations going forward in its ERISA plans.[3] (UBH's ERISA plans cover more than 20 million Americans.[3])

The district court's ruling in the *Wit* case has been a huge win for millions of Americans across the country seeking treatment for mental health and addiction disorders. The decision also sent a message to insurers that, under ERISA, they must decide whether care is medically necessary based on standards set by clinicians, not based on insurers' financial self-interest. The case has also spurred state-level action, including new laws in several states, such as California,[4] with the aim of preventing insurers from using medical necessity criteria that are inconsistent with generally accepted standards of care as well as to put in place a standardized definition of medical necessity.

Tragically, however, this huge win in *Wit* became a huge loss in March 2022, when a 3-judge panel of the federal Ninth Circuit Court of Appeals reversed the *Wit v UBH* decision.[5] It took a single paragraph of a cursory 7-page ruling—in contrast to the comprehensive, 100-page-plus district court decision—for the panel to reverse the district court and allow UBH to use medical necessity criteria that may be inconsistent with generally accepted standards of care.[5]

The appellate panel did not address any of the exhaustive evidence presented at trial or the district court's findings that UBH's criteria were consistent with generally accepted standards of care. The panel also ignored UBH's violations of several states' laws that are an important part of the case. These state laws required UBH to use the ASAM criteria (or criteria consistent with it) for substance use disorder determinations. The attorneys general of 3 of these states—Illinois, Rhode Island, and Connecticut—filed an amicus brief with the Ninth Circuit asking it to correct the panel's significant errors.[6]

If the panel's flawed reversal stands, it will have a ripple effect that undermines the health coverage of the more than 130 million Americans in employer-sponsored ERISA plans. The ruling effectively gives every insurer the green light to use whatever self-serving criteria it wishes when deciding whether to pay for treatment.

Furthermore, the reversal creates more obstacles to individuals who are struggling at a time of unprecedented need. Hardest hit will be those patients in ERISA plans with the least financial resources, who lack the ability to pay out of pocket for care. Already underserved low-income communities, LGBTQ+ communities, and communities of color will once again be disproportionately harmed, reinforcing our deeply inequitable system that rations care based on ability to pay.

The *Wit* reversal also directly harms clinicians' ability to properly care for their patients. Clinicians will be forced to spend more time trying to convince insurers that the treatments they select as most appropriate for their patients meet insurers' self-serving criteria, rather than independent, objective standards. The reversal also is an obstacle to clinicians providing care that is consistent with generally accepted standards. If insurers refuse to cover such care and patients

Poetry of the Times

Contemplating Retirement

Richard M. Berlin, MD

Patients get better, treatments end,
openings appear in my schedule
and I leave them open, like my window
in May when a seductive spring breeze
reminds me how much I want warmth's
embrace. I let my mind wander to new meds
I need to master, CME credits to earn,
the effort of starting with someone new—
telephone screening, establishing trust
and rapport, history-taking's excavation,
responsibility's weight, all the risks,
prior auths, and plagues of electrons
when IT systems change and a Help Desk
ticket is my only source of support.
Last week I changed my voicemail greeting
to declare I'm not accepting new patients,
but people don't want to believe me—

No one is taking on new patients
and I'm really depressed. Call me
when you have an opening.
I'll pay out of pocket.

Please put me on your waiting list.
I'm available any time YOU have time.
I've heard you're really good,
so I'll wait as long as I have to.

And the most perceptive caller,
sensing the ambivalent note in my voice,
asks what I've been asking myself—
So, you say you're not taking new patients.
Is that just for now, or is it forever?

Dr Berlin has been writing a poem about his experience of being a doctor every month for the past 24 years in *Psychiatric Times*™ the "Poetry of the Times" column. He is instructor in psychiatry, University of Massachusetts Medical School, Worcester, Massachusetts. His latest book is *Freud on My Couch*. ■

cannot afford appropriate care without coverage, clinicians are often put in an untenable position of negotiating with insurers for coverage for treatment that is not the most appropriate. Our laws should not permit insurers to insert themselves between clinicians and their patients.

With our country's ongoing mental health and addiction crisis, the consequences of the *Wit v UBH* reversal are too great to ignore. Indeed, this is why several dozen patient and provider groups, including the American Psychiatric Association and the American Medical Association, filed amicus briefs asking the Ninth Circuit to revisit this flawed ruling and grant the rehearing petition.[7]

If insurers are allowed to use whatever criteria they wish, millions of Americans will continue to be subject to arbitrary coverage denials that deny them a path to recovery. The Ninth Circuit must not neglect its duty by allowing insurers not to fulfill theirs.

Should the Ninth Circuit deny a rehearing, the only option will be to push legislation in states and in Congress to require insurers to follow generally accepted standards of care. Because clinicians are on the front lines of helping their patients get the mental health and addiction care they need, I encourage clinicians to join the effort to require insurance companies to make decisions in patients' best interests. Insurers should be competing on how best to improve their members' well-being, not on the efficiency of denying coverage.

Dr Insel is a psychiatrist and neuroscientist who has been a national leader in mental health research, policy, and technology. He is the author of *Healing: Our Path from Mental Illness to Mental Health*.

EDITOR'S NOTE: All information within this article was up to date at the time of print.

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From the Cover

At-Home Ketamine: A Clinician's Dilemma

including 9 infusions of intravenous ketamine over the years for his mental health symptoms, with mixed results. His current medications include aripiprazole 10 mg, desvenlafaxine 100 mg, clonazepam 0.5 mg QID, and mixed amphetamine salts 20 mg QID. Although his symptoms have improved and he is functioning well, he still reports some mild, low-grade depression and anxiety.

Mr Brad underwent a virtual assessment with a multistate licensed online health care provider (HCP) who was physically located in another geographic area. According to the patient, he shared his medical history, medications, and current symptoms. He was not asked to sign a release, and we were not contacted by the HCP. This presented a clinical dilemma as to our role, responsibility, and liability if we continued to treat the patient with these medicines while he was receiving at-home ketamine though another provider.

Prescribing Ketamine

There has been a recent proliferation of online health care businesses that offer at-home ketamine through virtual visits to patients suffering from a variety of mental health conditions. Ketamine is FDA approved for anesthesia and pain management but not for depression or any other psychiatric disorder.[1] HCPs in many countries, however, can prescribe ketamine off label for nonapproved indications.[2]

Ketamine can be rapid acting and studies have shown effectiveness in treatment-resistant depression (TRD), suicidal ideation, and other psychiatric conditions.[3,4] The therapeutic effects are often attributed to its antagonistic effects on the NMDA receptor, 1 of 4 subtypes of inotropic glutamate receptors located throughout the central nervous system.[5]

Ketamine is a dissociative drug with abuse potential. The dissociative and altered state seen with ketamine may play an important role in its therapeutic benefits. Increased attention in the lay literature and on social media on ketamine as a psychiatric treatment alternative, as well as a tool to facilitate psychotherapy through its mind-expanding properties, has led more patients to seek out this potential therapy, with or without their HCP's consent.

Simultaneously, there has been an uptick in utilization of online telehealth providers, particularly in mental health. This has been accelerated with technology advances, increased investor interest in this business model, and COVID-19 limiting in-office health care. These businesses claim to make mental health care more convenient, affordable, and accessible by offering care in locations with few mental health care providers.

Access to ketamine as a treatment option can be challenging to interested patients. Many HCPs are reluctant to suggest or use ketamine since it is not approved for psychiatric conditions. Psychiatrists more accepting of ketamine as a treatment option may not have the staff, space, training, or equipment to administer the medication in their offices. Nonpsychiatric health care practitioners including anesthesiologists, mid-level anesthetists, and other HCPs may be skilled at ketamine administration but not in managing patients with treatment-resistant psychiatric disorders. Ketamine therapy can be costly since it is often not covered by insurance.

Esketamine has some similar pharmacokinetic and pharmacodynamic properties to ketamine since it is an isomer of the medication and is FDA approved for TRD and major depression with suicidal ideation. Access to esketamine is limited since many insurances are reluctant to approve this treatment. Few mental health practitioners offer this treatment since they do not have the office space, comfort level, or ability to navigate the complex insurance obstacles restricting payment.[6]

Recently, several telehealth companies have emerged offering virtual assessments and at-home ketamine delivery, including but not limited to Mindbloom, My Ketamine Home, and Smith Family MD.[7-9] These companies specifically market to those looking for ketamine treatment. While promoting at-home ketamine for treatment of psychiatric disorders, many of these companies are led by medical directors without mental health training. Mindbloom, one of the largest such virtual, at-home services, does have psychiatric physicians on its leadership team, including 2 chairmen and vice chairmen of psychiatric hospital departments and a former chief medical officer of the US Department of Health and Human Services.[7]

In 2008, the Ryan Haight Online Pharmacy Consumer Protection Act was passed after a 17-year-old boy died of an opiate overdose prescribed through a telemedicine consult.[10] This law limited the prescribing of controlled substances through telemedicine consult without a face-to-face encounter and an adequate medical evaluation. In 2021, with COVID-19 affecting in-person health care, the Drug Enforcement Administration temporarily loosened the prescribing restrictions of Scheduled II-V controlled substances (CS).[11,12] There is a legislative push to continue these lessened restrictions post-COVID.[13]

CASE VIGNETTE 2 "Mr Ryan" is a 65-year-old man who agreed to be interviewed regarding his experience with at-home oral ketamine prescribed through an online provider. Mr Ryan has suffered from dysthymia and mild anxiety without much relief from medication or counseling. He has used psychedelics including LSD, psilocybin, and mescaline for spiritual growth and as a mind-expanding practice. He denies any history of recreational drug use. He reached out to 1 of the telehealth companies offering at-home ketamine after reading an article about the potential benefits of this therapy.

He paid an upfront fee for a package, which included an initial online meeting, follow-up, and exit assessment with a nurse practitioner (NP), 2 sessions with a ketamine "guide," 6 doses of oral ketamine, and a kit that included a blood pressure cuff, eye mask, educational resources, journal, pen, and audio program to listen to during dosing.

The initial assessment was conducted virtually over 30 minutes in which he was asked about his symptoms, drug experiences, height, weight, medical history, and expectation of treatment. He had to show his blood pressure reading from his cuff. He was not asked to share his health care providers' names, to sign releases for his HCPs, or to provide any blood work.

He was then sent 450 mg of oral dissolvable ketamine to his home. On the day of dosing, he had a virtual session with his guide during which he was told what to expect during dosing and how to take the medication, given therapeutic readings, and instructed to set an intention for the experience. He had to show his blood pressure readings and have someone else in the home with him before dosing. The guide was not online during the entire session but was available if needed. Mr Ryan was instructed to check in 1 hour after dosing.

Mr Ryan experienced a moderately high level of dissociation with no significant adverse effects. He found it to be pleasant and therapeutic. He had a follow-up visit with the prescribing nurse practitioner a few days later and was then sent all 5 remaining treatments at 750 mg per dose. He met virtually with the guide for the second session. During the last 4 sessions, he was not required to show any more blood pressure readings or to meet with the guide or the NP. He had unlimited access to the guide via texting if he desired.

After his sixth treatment, Mr Ryan had a virtual exit visit with the NP and was offered another 6 doses without a guide for a lower fee. He could pay extra for the guide as well as for an audio program for depression, anxiety, or self-esteem. Although his experience was positive overall, he did have some concerns about the level of monitoring. He would prefer an in-person, more closely supervised experience if it was affordable and available in a warm, therapeutic setting rather than a sterile, medical office environment.

TABLE. Bioavailability Comparison: Routes of Ketamine Administration

Route	Intravenous ketamine	Intramuscular ketamine	Intranasal ketamine	Sublingual ketamine	Oral ketamine
Bioavailability	100%	93%	45%	30%	17%-23%
		With intraindividual variability			

The Risks of At-Home Ketamine

At-home ketamine treatment initiated by an online provider presents many legal, clinical, and ethical challenges to HCPs and potential risks to patients. Some legal questions are whether online prescribing of ketamine, a Schedule III medication, meets criteria for the looser rules of prescribing a CS without an in-person examination, particularly if ketamine is being used for a mind-expanding, emotionally cathartic purpose. The current law states that the prescription must be for a legitimate medical purpose by a practitioner in their usual course of their professional role.[12] Whether this meets that definition could be an area of debate. Additionally, by continuing their psychiatric medications and other treatment while they are receiving at-home ketamine, is a clinician giving consent to this treatment? Is a clinician liable if there are complications or drug interactions with a medication they are prescribing during at-home ketamine administration?

Issues of safety evoke clinical questions as to who should be prescribing concomitant psychiatric medicines during ketamine use. There may be medical and/or psychiatric changes related to ketamine dosing that could require alterations in the medication regimen. Although most side effects of ketamine are mild and transient, there are potentially serious safety concerns including elevations in blood pressure, anxiety, severe dissociation, delirium, mania, and psychosis.[14] Long-term risks of therapeutic ketamine dosing remain unknown.

Although there are no specific guidelines for off-label ketamine administration, there are standards of care that often include a dosing range based on weight, a medical screening that typically includes baseline blood work, and, in many cases, drug screens and an EKG, along with coordination of care with the patient's HCPs. Most clinicians dosing ketamine will follow blood pressure, pulse, and, in some cases, pulse oximetry and cardiac monitoring by a trained health care professional during each treatment. Esketamine shares many of the same risks as racemic ketamine and was approved with the restriction that it could only be administered under a Risk Evaluation and Mitigation Strategy (REMS) program.[15] REMS is for certain medications with serious safety concerns to help ensure the benefits outweigh the risks. There is required registration and training for the patients, HCPs, and pharmacists. There is a 2-hour minimum observation by a medical professional and blood pressure monitoring in office with a prescriber onsite.

At-home ketamine treatment initiated by an online provider presents many legal, clinical, and ethical challenges...

With the self-administration and availability of multiple dosing with at-home ketamine, there is an opportunity for intentional or unintentional overadherence and overdosing. There is a risk with combining at-home ketamine with alcohol or drugs of abuse including opiates, amphetamines, or benzodiazepines, or with legitimately prescribed medications that could have serious and life-threatening interactions.

This also raises questions as to whether oral ketamine is even efficacious in the treatment of any psychiatric condition. Ketamine been most studied with intravenous administration starting at doses of 0.5 mg/kg. There are only 2 randomized control studies looking at antidepressant efficacy of oral ketamine in which much lower doses were used than those given by many online prescribers.[16] Most other studies are small case reports and series.[17] Oral ketamine has low and varied bioavailability (**Table**), leading to questions such as what is the safe and effective dose to prescribe?[18] Additionally, ketamine is a drug of abuse with street value. Online practitioners sending multiple doses at once puts the patients at risk of overdose, abuse, and diversion.[19]

Concluding Thoughts

We made the decision to notify Mr Brad that we did not agree with his decision to undergo at-home ketamine. Our concern was whether this was an appropriate treatment for him and what we perceived was inadequate at-home monitoring. Furthermore, we were not comfortable with the concomitant use of benzodiazepines and high-dose stimulants. We suggested that if he was going to continue this treatment against our recommendation, he taper off both of those medications. We informed him that we felt it was unsafe for us to continue managing his psychiatric medications while he was self-administering ketamine at home.

This case illustrates an important issue that clinicians will likely soon confront (if they are not encountering it already). Although at-home ketamine is a reality for now, it is conceivable that similar issues may arise with other off-label or unproven therapies, including the much-hyped psychedelic medicines, becoming available to our patients. Access to these therapies, even when illegal, is becoming easier, and government agencies, medical regulatory bodies, and clinicians need to be prepared to manage these situations as they arise.

Dr Banov is a psychiatrist at PsychAtlanta/PsychAtlanta Research Center and on the faculty in the Department of Psychiatry at the Medical College of Georgia. Dr Banov reports disclosures as a speaker for AbbVie, Supernus, Janssen, Intracellular Therapies, and Teva. **Ms Landrum** is an MD candidate at the Louisiana State University Health Sciences Center.

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PAYER PROVIDER PERSPECTIVES

Exploring DTx for Clinical Care

Heidi Anne Duerr, MPH

Digital therapeutics (DTx) have the potential to expand access and to provide options to patients, as well as improve treatment feedback, agreed panel members in the recent *Payer-Provider Perspective: Prescription Digital Therapeutics* custom video program.

Evidence-Based Care

When discussing DTx, whether with patients or colleagues, it is important to stress that these products are evidence based, the expert panel members said. This is especially true considering the number of options and tools available, added Timothy Aungst, PharmD, associate professor of pharmacy practice at the Massachusetts College of Pharmacy and Health Sciences in Worcester and a clinical pharmacist at a home health care agency.

"You open up your smartphone, and you look up something in the app store, and you are going to get hit with a lot," Aungst said. "There are 300,000-plus health and medical apps out there, and no curation. So, how do we know this stuff actually works? How do we go from the consumer model where we say, 'Sign up for a subscription, download this thing, it is going to do something for you'? Well, how do you know it is actually going to do something for you? And here is the key thing: We want evidence to show. We want to be able to say in which patients they do work, or how much time do you need to achieve is a set outcome." Having that information—efficacy evidence—is important, he said.

Some apps and DTx are approved by the FDA, the group noted, which lends additional credibility. Yet, lack of FDA approval may not necessarily mean a particular DTx is not worthwhile, the panel agreed. This further complicates matters, as there are discussions among payers regarding what level of evidence or approval is needed for coverage and reimbursement. The more evidence, the better, they all agreed.

Improving Access

According to the panel, DTx improves access to care in several ways: It improves care availability when the support is most needed; it makes care more convenient; and it extends care despite a shortage of clinicians.

One of DTx's strengths is that it can reach patients where and how they are most comfortable, explained Aungst. Just as ease and convenience have influenced people in other areas of the economy, point of care matters, he added. He posed the questions patients may ask themselves: "Do I want to spend time driving to someone to provide the care, or do I want this on my own time?... Do I have to go to a clinic to get this done? Does it mean I have to ask for time off in the day, and will my employer get angry? What am I going to do about childcare? Versus the alternative: Can I do this on my own, and guide it in a way?" The flexibility and convenience of DTx allows patients to fit the care into their schedules as they need it, he said.

Panel moderator John Fox, MD, principal of Foxworthy Healthcare Consulting, agreed, noting that need can occur outside of normal office hours. By having DTx as an option, patients can access the care and support as they need it. "Often, patients use these [DTx products] when they need it the most, and when you need it is not 8:00 scheduled on a Tuesday morning appointment with your psychiatrist," he said.

Arwen Podesta, MD, a board-certified adult psychiatrist in New Orleans with subspecializations in addiction medicine, forensic psychiatry, and integrative medicine, uses DTx primarily for opioid use disorder, alcohol use disorder, polypharmacy use disorder, and insomnia. When she introduces DTx to patients, she provides them with an overview, then suggests they delve further at home. This encourages its use at home when busy patients find it most convenient.

Health Care Inequities

Convenience is not the only access issue. The challenges of health care disparities were "painfully underscored" by the COVID-19 pandemic, said Scott Whittle, MD. A child and adolescent psychiatrist by training, Whittle is a physician at Intermountain Healthcare and medical director at SelectHealth in Salt Lake City, Utah.

"At least to some extent, health care equity is nowhere where we thought it was, and the gaps between who has access and who does not, who has access to engagement and who does not, have been made painfully clear," Whittle added. "Beyond that, I think that [the lack of equity has] accentuated the human resource crisis we are facing nationally in terms of just simply having the human resources to apply to the problem as a whole."

Not surprisingly, Whittle estimated that access to care for behavioral health conditions ranges between 10% and 40% to 50%. As an example, Whittle said that Intermountain Healthcare recognized that if they "didn't double access to behavioral health care services within the next 3 to 5 years, we would be seeing a further deterioration of our ability to meet these needs. Not just hold steady—further deterioration."

Not only are there not enough resources in some areas, but the panel also agreed there are health care deserts—areas of the country that completely lack behavioral health care clinicians—that would especially benefit from the use of DTx.

Although some people do not believe DTx is the next best thing in health care, it is hard to deny its potential, Whittle added. "It is going to have the access scalability to meet your patients where they're at, because otherwise, they are not going to see anyone. And we do not know if that will lead to traditional end points of concern, like [emergency depart-

To watch this and other *Payer-Provider Perspectives custom* programs visit *psychiatrictimes.com/view/understanding-dtx-and-pdts*

ment] visits, hospitalizations, and a downstream cost."

In fact, in a recent meeting, a senior medical director of a behavioral health care system said to Whittle, "We need to be putting DTx at the front end of care, not at a carefully guarded back end, because the access crisis is real."

Alternative, Discreet Options

DTx also can offer patients additional or alternative support to psychopharmacological options. Some patients do not fully remit with psychopharmacology alone, and other patients may be reluctant to rely on medications. This is especially true in child and adolescent populations; parents often have concerns about their children using psychopharmacological agents. For these patients, DTx provides access to care via a safe and effective alternative.

"As a pediatrician, I knew that a lot of parents did not want to treat their kids' ADHD [attention-deficit/hyperactivity disorder] symptoms with medication," said Whittle. "So the fact that this is a therapeutic without being a medication has appeal, either as a standalone or as an ancillary approach."

This may be especially true of the latest FDA-approved video game indicated for addressing symptoms of ADHD, added Podesta. She noted that parents of children with ADHD "want it badly."

Additionally, the stigma attached to receiving psychiatric care can prevent patients from seeking it. DTx can provide discreet, convenient care and support, Whittle said.

Improving Engagement

According to Fox, another advantage of DTx is "getting real-time or near real-time feedback, both to the provider and the patient." Most DTx have both patient and clinician portals, allowing clinicians to monitor DTx use and symptom improvement.

Podesta agreed. "What we do not get with traditional pharmacotherapeutics or with other prescribed or recommended therapy, such as outpatient therapy, is numbers—data," she said.

Not only do data help to show adherence, but they also shed light on outcomes, Podesta added. This benefits her, as the clinician, as well as her patients. Podesta always tells her patients that she will be monitoring the clinician platform of the DTx, an arrangement she finds that most patients like. "They tend to be more excited and feel more accountable," she explained.

The lack of similar engagement with psychopharmacological options could be driving the failure of treatment as usual, said Whittle. From a claims-based perspective, "Starting a prescription for medication-assisted treatment or asking somebody to go to therapy usually fails between 7 and 9 times before [the suggestion] sticks. Seven to 9 times," he emphasized. "Somebody's struggling with, say, the condition of depression, opiate use, or alcohol use disorder, and when somebody's struggling with that, it is not the moment in the therapist's office that we are trying to manage. It is that individual feeling connected enough to build recovery capital on a longitudinal basis. And quite frankly, nothing accomplishes that better than the digital strategies that are available."

Podesta agreed about the need for engagement and how DTx can help improve that, especially through text messaging. Plus, DTx empowers patients and gives them an extra degree of support. Patients, she has found, appreciate "the use of the apps to augment and overcome specific disease states and symptoms."

In addition, the DTx programs Podesta uses most often leverage contingency management, which has been proven to be very effective. This gives patients 2 support systems rolled into 1. "At 4:00 AM, they wake up thinking that they want to go get drugs to help them go back to sleep or to calm their nerves. And then they use that app that I have been so clear is part of their care. [After using the app], they get an Amazon gift card or whatever it is, and then more salience occurs to get them to do it again. So, it is forward-thinking."

Concluding Thoughts

The panelists expressed hope that their colleagues, patients, and payers recognize how DTx can be a powerful tool in behavioral health care. Specifically, Podesta said she would want her colleagues to know "prescription digital therapeutics are evidence-based, research-based, effective tools to improve outcomes. We have new technology coming down the pipeline every day—why not use it therapeutically to actually better help patients?...Their safety is beyond [that of] almost any prescription that I have ever written as a psychiatrist. And, with a lot of my patients not wanting to be on medicines, using these tools is a game-changer."

"DTx offer solutions in a number of very challenging spaces and access—access to care is incredibly challenging," added Whittler. "DTx offer the engagement element that traditional treatment has really struggled to provide, [plus] they offer [the data and support showing] the treatment being provided is actually evidence based." ●

Psychiatric Times™ Conference

Clinical Pearls, New Research

Leah Kuntz

Leaders in psychiatry from across the country gathered in San Diego, California, for the 2022 Annual *Psychiatric Times*™ World CME Conference. For maximal flexibility for attendees, the conference was available via a live virtual platform as well as in person. As in previous years, the conference's signature format of 20-minute interactive presentations allowed for coverage of a range of topics, including advances in the field, overcoming diagnostic challenges, and new and novel treatment strategies. In addition to the presentations, in-person attendees had the opportunity to discuss issues and ask questions in small groups, including a Meet the Editor Breakfast.

Managing Psychiatric Disorders During Pregnancy and Postpartum

"We always want to make sure we weigh the risks of the untreated psychiatric disorder when we are considering treatments, especially medication exposures, for women of reproductive age," Marlene Freeman, MD, professor of psychiatry at Harvard Medical School, told attendees.

In her presentation "Pregnancy and Postpartum Management of Psychiatric Disorders," Freeman discussed the importance of focusing on antidepressant treatment in women with depression during their reproductive years. Approximately 45% of pregnancies in developed countries are unplanned, Freeman shared, and 75% of teen pregnancies are unplanned.[1] Furthermore, 82% of US women have had a child by aged 40 years.[1] This is why it is important to tend to psychiatric disorders, which carry risks for both mother and baby if left untreated.

"The risks of the untreated psychiatric disorders impact efficacy and outcomes as well as child development overall," Freeman said.

Freeman also explained the absolute risk of selective serotonin reuptake inhibitor (SSRI) exposure in pregnancy is small, and reproductive safety data on SSRIs exceed what is known about many other medications used in pregnancy. Prevalence of SSRI use during pregnancy is 3% to 7%, she added.[2-7]

Antidepressant Use and Risk. According to recent research, there is no evidence of increased risk for major malformations or cardiovascular malformations in the offspring of women who took SSRIs while pregnant.[8]

Another concern heard about SSRIs is the potential increased risk of autism. However, Freeman shared that studies and meta-analyses results indicating an association of SSRIs with increased risk of autism is not by cause and effect; maternal psychiatric illness must be factored in, she said, and that appears to be the driving factor.[9]

Treatment Recommendations for Postpartum Depression. "Postpartum depression has been called the most common obstetrical complication," Freeman told attendees. Approximately 10% to 15% of women experience major depressive episodes post-delivery, and that number increases to 25% to 40% if the woman has a history of major depressive disorder, she explained.

Freeman had a number of tips for treating mothers with postpartum depression, including using the lowest effective doses of SSRIs, consulting with perinatal/reproductive psychiatry specialists as needed, and maximizing nonmedication treatments. Nonpharmacologic strategies include maximized social supports, psychoeducation of patient and family, group therapy or support groups, interpersonal therapy, and cognitive behavioral therapy.[10-12]

The Massachusetts General Hospital Center for Women's Health hosts additional resources for clinicians and their patients on its website (www.womensmentalhealth.org), Freeman added.

"There are a lot of unknowns involved with pregnancy," Freeman concluded. "We want to make sure that the treatment decisions we make are really collaborative with patients."

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Childhood Trauma:
10 Tips for Screening and More

In his presentation "How to Assess/Diagnose Childhood Trauma," Mark B. Hamner, MD, pointed out that Department of Health and Human Services data on child abuse underestimate traumatic exposure because they addressed only abuse and not other traumas. "And abuse is often not reported," he added.

Children can experience a number of traumatic experiences beyond physical, sexual, or psychological abuse and neglect, said Hamner, including natural disasters or terrorism; family or community violence; the sudden or violent loss of a loved one; substance use disorder either personally or within their family; refugee and war experiences, including torture; serious accidents or life-threatening illness; and military family–related stressors, like deployment or parental loss. All can play a part in the child's traumatic history.

Additionally, in the National Comorbidity Survey Replication Adolescent Supplement, which looked at a national survey of adolescents aged 13 to 17 years, the lifetime prevalence of DSM-IV posttraumatic stress disorder (PTSD) was 4.7% higher in girls.

Children and adolescents who identify as part of the LGBTQ+ community experience trauma at unique, higher rates. Common traumas include bullying, harassment, traumatic loss, intimate partner violence, physical and sexual abuse, stigma, and more.

"Somatization is a significant posttraumatic stress symptom," added Hamner. "Some have argued this should be included in diagnostic criteria."

An exemplifying study looked at the relationship between PTSD symptoms and somatization and between intelligence and somatization in child sexual abuse victims to determine whether the type of abuse had an effect on the relationship between PTSD symptoms and somatization.[1]

The study concluded that somatization in children who were sexually abused was influenced by the severity of PTSD symptoms and intelligence and the effect of the PTSD symptoms on somatization was moderated by type of abuse.

When screening children and adolescents for trauma, Hamner shared a few tips that might help:

1. Make time in therapy sessions to complete screening measures with family members.
2. Allow the parent and child to choose the language in which the screen is completed.
3. Use developmentally appropriate strategies, like a chalk or dry erase board.
4. Let them decide the order in which they complete measures when possible.
5. Use visual aids.
6. If the child is resistant, read aloud to them.
7. Offer to complete over 1 to 3 sessions.
8. Praise all children and parents for "hard work."
9. Check endorsement of critical items like hurting oneself and develop a safety plan.
10. Take time to explain what will happen next and clarify that you will readminister measures on an ongoing basis.

The National Child Traumatic Stress Network is an important resource, Hamner also noted. Specifically, he mentioned the Child and Adolescent Trauma Screen (CATS) instrument, as it is downloadable and brief, taking only 5 to 10 minutes to complete.[2] This could be a helpful tool in the screening arsenal, he said.

"There are unique developmental considerations in this age range," Hamner concluded. "It's a vastly under-researched area, not only in terms of epidemiology but also in terms of treatments."

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Trauma in the DNA:
Educator of the Year Lecture

"Real true, posttraumatic stress disorder [PTSD] is going to have an impact, certainly on the next generation and maybe generations after that," said Rachel Yehuda, PhD. Yehuda, who was named Educator of the Year, shared her research on the potential genetic passing of PTSD through generations.

Previous research by Yehuda et al showed adult offspring of Holocaust survivors had differential effects of maternal and paternal PTSD in both glucocorticoid receptor sensitivity and vulnerability to psychiatric disorder. With both maternal and paternal PTSD, offspring had lower GR-1F promoter methylation; with just paternal PTSD, offspring had GR-1F promoter hypermethylation.[1] Furthermore, Holocaust exposure induced intergenerational effects on FKBP5 methylation; specifically, Holocaust survivors and their adult children showed a non-genotype-dependent change in methylation compared with their respective controls.[2] This was the first demonstration of an association of preconception parental trauma with epigenetic alterations that is evident in both exposed parent and offspring.

Similar findings resulted from Yehuda's work on the effects of 9/11. For example, in a post-9/11 program surveilling women who were pregnant, Yehuda et al collected salivary cortisol from mothers and babies.[3] "What we found is that the mothers who felt PTSD, their cortisol levels were lower, but it's also lower in babies, which was really wild," said Yehuda. "But here's the kicker: Both cortisol levels are lowest in the babies of mothers with PTSD who were exposed in the third trimester."

This research suggests maternal PTSD may confer additional in utero effects, causing more anxiety.[3] Trauma exposure during pregnancy directly affects the fetus and fetus germ cells, Yehuda shared.[3]

Yehuda explained that epigenetic changes could survive cell division associated with the formation of sperm and eggs; if the parent is exposed to trauma, their exposure could result in epigenetic changes that may affect their sperm or egg—meaning a single trauma could simultaneously affect multiple generations without direct exposure.

"This is inherited in our DNA," said Yehuda. "Trauma is inherited."

The biological remnants of parental experiences in our DNA can affect us in multiple ways, according to Yehuda. They can influence our response to stressors/challenges, make us better able to detect and respond to threats, increase vulnerability to mental health disorders, and increase our attunement to injustice. They are enduring, but not irreversible, Yehuda stressed.

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INTEGRATIVE MEDICINE SPECIAL REPORT

Complementary, Alternative, & Integrative Approaches in Mental Health Care

James Lake, MD

Psychiatry, as conventionally practiced, is being influenced by increasing openness to non-Western healing traditions in the context of accumulating research evidence for select complementary and alternative medicine (CAM) modalities and growing demands for more personalized care. Individuals who seek psychiatric care for depressed mood, anxiety, and other common mental health issues are increasingly concurrently seeking CAM options via Chinese medical practitioners, naturopathic doctors, herbalists, chiropractors, homeopathic physicians, energy healers, etc.[1] At the same time, increasing numbers of physicians are being trained in CAM approaches and incorporating CAM into their medical practice.[2]

Collectively, these trends have resulted in rapid growth of integrative mental health care, a collaborative care model that incorporates modalities from psychiatry and CAM and focuses on the whole person; one that has the dual objectives of optimizing well-being and treating specific mental health problems.

This *Psychiatric Times*™ Special Report contains concise reviews of selected CAM modalities. In addion, this issue's continuing medical education article reviews CAM interventions for mental health problems associated with the COVID-19 pandemic. The CME article reviews and discusses progress on CAM interventions for enhancing resilience and well-being during prolonged periods of social isolation during lockdowns, and for treating depressed mood, anxiety, and other mental health problems associated with the pandemic.

For instance, data from studies of the neurobiological mechanisms of mind-body medicine support the notion that mind-body practices (eg, tai chi, qigong, yoga, and meditation) enhance general well-being and alleviate symptoms of stress, anxiety, depressed mood, and other common mental health problems These beneficial effects are mediated by neural and physiological mechanisms. As you will read, further research is needed to determine which interventions are most effective for specific disorders and to identify the physiological and neural processes that mediate beneficial effects.

The use of herbals is another common practice that is noted in this Special Report. Widely used herbals typically have bioactive components that mediate complex effects involving multiple neurotransmitter systems; regulate gene expression; and have anti-inflammatory, antioxidant, or endocrinologic effects. In contrast, psychotropic medications are synthetic molecules designed to have discrete modulatory effects on specific neurotransmitter systems.

There is evidence that patients with posttraumatic stress disorder and complex trauma also leverage integrative medicine and nutrition. Dietary modification, nutraceuticals, hydrotherapy, exercise, body-centered therapies and sleep hygiene, and psychedelics are among the 17 components of integrative approaches to PTSD.

Although these pieces just scratch the surface of CAM use in psychiatry, hopefully it provides you with preliminary insights and inspiration.

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Dr Lake is a board-certified adult psychiatrist with more than 25 years' clinical experience. He is an adjunct fellow at the National Institute of Complementary Medicine Health Research Institute, Western Sydney University, Australia. He founded and chaired the American Psychiatric Association's Caucus on Complementary, Alternative and Integrative Medicine from 2004 through 2010, and has chaired symposia and workshops at American Psychiatric Association conferences and other national and international conferences on complementary, alternative, and integrative mental health care. Dr Lake is the author or editor of 5 textbooks on alternative and integrative mental health care and a 10-volume series of self-help books on alternative and integrative treatments of depressed mood, anxiety, attention-deficit/hyperactivity disorder, bipolar disorder, and other mental health problems.

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Exploring Integrative Medicine and Nutrition for PTSD

Leslie E. Korn, PhD, MPH

Evidence from a growing number of studies suggests that 38% to 40% of adults living in the United States use complementary and alternative medicine (CAM) therapies,[1] yet only 42% have told their primary physician that they do so.[2] Patients do not disclose their use for numerous reasons. They are not asked about it; they are concerned that their clinician will disapprove; they may not think it is necessary; and/or their clinicians are not interested in or do not know about CAM methods.[3] Moreover, integrative medicine (IM) appeals to groups like veterans who traditionally avoid or experience dissatisfaction with conventional treatment and are prone to posttraumatic stress disorder (PTSD).[4] Hence, clinicians should disclose their interest and training in IM and ask patients about their health practices.

Integrative medicine and nutrition for the treatment of PTSD is comprised of 18 components (**Table 1**).[5] To best support patients, clinicians should individualize their approach based on patients' needs and preferences.

Digestion, Nutrition, and PTSD

Stress and trauma affect all aspects of physical function: blood glucose levels, brain metabolism, energy, and altered brain structures where neurons misfire or fail to communicate. When stress dysregulates digestion, it leads to a cascade of events affecting mood, cognition, sleep, and immune function. Parasympathetic activity governs digestion, which explains why in PTSD and complex trauma, there is at least 1 associated digestive problem. In sympathetic arousal, the head hurts, the stomach aches, and the intestines are too active or immobilized by fear. Irritable bowel syndrome (IBS) often co-occurs with traumatic stress, and chronic gut distress can lead to PTSD.[6] Similarly, there is a causal chain that links childhood abuse, dissociation, and somatization with IBS.[7]

These often-explicable somatic symptoms represent a complex neuroimmunomodulatory communication system between the gut and the brain. Gut bacteria regulate the hypothalamic-pituitary-adrenal (HPA) axis[8] and γ-aminobutyric acid (GABA) via the vagus nerve,[9] which reduces anxiety and depression.

Patients should consider increasing healthy intestinal bacteria by eating fermented foods (eg, yogurt, kefir, kimchee, kombucha, sauerkraut, and stink eggs) or via supplementation with high-dose probiotics. Probiotics have been associated with pain reduction, suggesting an anti-inflammatory effect.[10]

Nutraceuticals and Supplements

Nutritional medicine, diet, and nutraceuticals are increasingly used in psychiatry.[11] Vitamin D,[12] omega-3 fatty acids,[13] antioxidants (eg, vitamin C, vitamin E, and zinc), folate, magnesium, and vitamins B_6, B_9, and B_{12} can provide core nutritional support for mental health.[14] Phospholipid supplements have been found to reduce circulating cortisol, improve memory, prevent cognitive decline, and improve perceived well-being.[15] Phosphatidylserine (PS) and phosphatidylcholine (PC) are concentrated in brain cell membranes and support cell structure and function. PS aids neurotransmitter activity, especially dopamine and acetylcholine, and supports cognitive function.[16]

Mitochondrial Health

Brain neurons have a high demand for adenosine triphosphate (ATP),[17] and their high oxygen consumption rate leads

TABLE 1. The 18 Components of Integrative Medicine and Nutrition for the Treatment of PTSD[5]

1. Bioindividuality
2. Integrative assessment
3. Circadian and biological rhythms
4. Culture and identity
5. Nature
6. Human—animal relationships
7. Digestion
8. Culinary medicine
9. Nutraceuticals
10. Herbal medicine
11. Hydrotherapy
12. Detoxification
13. Exercise
14. Somatics and bodywork
15. Breathing
16. Spirituality, meaning, and purpose
17. Altered states
18. Adherence

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to free radicals and inflammation, which benefit from antioxidants. Mitochondria may be affected by lack of sleep, pesticides, pollutants, antibiotics, and psychotropic drugs, including selective serotonin reuptake inhibitors (SSRIs).[18] Medications that are commonly prescribed to patients with PTSD (eg, statins, beta-blockers, neuroleptics, and corticosteroids) interfere with mitochondrial function, and mitochondria also suffer degradation as part of the aging process. Mitochondrial biogenesis may benefit from CoQ10, pyrroloquinoline quinone, quercetin, and carnitine.[19]

High-intensity aerobic exercise and photobiomodulation (PBM) also enhance mitochondrial biogenesis. Exercise enhances cognition and neuroplasticity, balances HPA function, reduces inflammatory markers,[20] and increases brain-derived neurotrophic factor (BDNF).[21] Anaerobic exercise builds core muscle strength and lean body mass; increases metabolism, glucose uptake, and energy; and improves sleep and anxiety in individuals with PTSD.[22]

The energetic exercises qigong and tai chi have been used with survivors of torture and have improved well-being and the quality of life in individuals with fibromyalgia.[23] Yoga has been found to increase levels of gamma-aminobutyric acid in the brain.[24] In one study, for example, African American female veterans who practiced 10 weekly classes of trauma-informed yoga experienced significant reductions in PTSD symptoms.[25]

Research on PBM in individuals with traumatic brain injury (TBI), PTSD, anxiety, and sleep disorders showed improvements following treatment, with a medium to large effect in major depressive disorder.[26-28] One animal study found that PBM treatment applied immediately after a traumatic event can prevent the development of PTSD-like fear.[29]

Bodywork and Somatic Therapies

There are as many systems of touch therapies as there are psychotherapies. Individuals of all ages are candidates for touch during all stages of their recovery. Different techniques of touch therapies facilitate specific responses. Bodywork and massage are also types of passive exercise that can help jumpstart activity and movement when the patient is not yet physically active. Stretching, range-of-motion rotations, pressure points, and guided breathing all reduce dissociation and begin the process of inviting individuals back into their bodies.

Massage and bodywork can decrease depression and anxiety; they have been used in children with PTSD following Hurricane Andrew,[30] in female survivors of sexual abuse,[31,32] and in individuals with a history of trauma who are caregivers to patients with dementia.[33] Rocking is a universal behavior that synchronizes the brain, accelerates and improves sleep quality, and increases sleep spindles, which are associated with being able to sleep through environmental noise.[34] Continuous rocking strengthens deep sleep via the neural entrainment and enhances memory consolidation during sleep.[35]

TABLE 2. The Criteria of Adaptogenic Herbs[46]

1. They should generally be free of adverse effects.
2. They should be nonspecific—that is, they should increase resistance to a wide array of physical, chemical, and biological stressors.
3. They should be able to normalize function and restore homeostatic balance.

Sleep

There is evidence that improving sleep should be a key component in addressing PTSD,[36] and nutritional interventions that target the HPA axis and circadian rhythm may be helpful. Lithium orotate is core support that lengthens circadian rhythm, balancing mood, sleep, and cognitive health. A suggested dose of 10 to 40 mg daily of lithium orotate combined with methyl folate can prove beneficial.[37] Combining bright-light exposure in the morning with vitamin B_{12} (methylcobalamin) can also help balance the circadian rhythm. Methylcobalamin enhances the light sensitivity of the circadian clock at dosages ranging from 1000 to 6000 mcg daily.[38]

Botanical Medicines

Individuals with PTSD may use cannabis to initiate sleep,[39] but the literature on this has mixed results. Generally, high ratios of tetrahydrocannabinol (THC) to cannabidiol (CBD) may exacerbate insomnia, whereas higher CBD or cannabinol (CBN) may aid sleep. Some individuals benefit from a 5-parts CBD/CBN:THC 5:1 or 10:1 ratio. If pain affects sleep quality, THC has a more anti-inflammatory effect, used in a 1:1 or 5:1 ratio.[40,41]

Lifetime cannabis use is more than 3 times more likely in individuals with PTSD than in those without.[42] This may be due to the part cannabinoids play in helping the body regulate the extinction of conditioned fear as well as in reducing pain and anxiety.[43,44] Low-dose THC in cannabis appears to have anxiolytic effects, whereas a high dose may be responsible for producing anxiety. Low doses reduce depression; high doses increase depression.[45]

Adaptogens

Adaptogens and their active extracts support HPA axis function build endurance, support immune function, and reduce fatigue. Adaptogens increase cellular respiration, aiding mitochondrial function. **Table 2** lists the 3 criteria of adaptogenic herbs.[46] Common adaptogens include Panax ginseng, eleuthero (also known as Siberian ginseng), and licorice root. Ashwagandha is called the queen of Ayurveda and has been used for more than 6000 years to enhance vitality and endurance. Rhodiola (*Rhodiola Rosea*) is the major botanical approved as an adaptogen by the Committee on Herbal Medicinal Products at the European Medicines Agency. It is a mild antidepressant and a stimulant that has been found helpful in addressing anxiety symptoms. Rhodiola is also anti-inflammatory, and it supports cognitive function. All these qualities make it a good option for supporting individuals with complex trauma and TBI.[47]

Sedative Botanicals

Kava is one of the most effective botanical nervines that functions like an anxiolytic. Like benzodiazepines, kava acts on the amygdala, reducing fear and anxiety, and it is also a muscle relaxant that improves cognitive performance.[48] Although kava-containing supplements have been associated with liver injuries, the aqueous extract of kava is safe; it is associated with no serious adverse effects and has no clinical hepatotoxicity.[49,50] Skullcap (*Scutellaria lateriflora*) acts on benzodiazepine receptors, is anti-inflammatory, and may be beneficial for anxious depression.[51]

Detoxification

In addition to eliminating harmful substance use, detoxification strategies can range from eliminating gluten from the diet to increasing cruciferous vegetables. The association between gluten, depression, and addiction is well established.[52] Cruciferous vegetables enhance P-450 enzymes and aid liver function in individuals in alcohol and drug recovery or who have been exposed to environmental toxins.[53] Detoxification also extends into cultural rituals like sweat lodges, temazcales, and saunas, which may decondition autonomic reactivity, increase adaptive immune function, and enhance bonding and attachment behaviors.[54]

Psychedelic Medicine

Psychedelic medicines alter the chemical transmissions and normal functions in the nervous system, leading to altered states and often transcendent or mystical experiences that may have import for the loss of hope, meaning, and purpose experienced by individuals with PTSD. These "psychointegrators" enhance the processing of essential information regarding self, emotions, social relations, and attachment behaviors, and facilitate this integration in the brain.[55] Psychedelics alter functional connectivity and can potentially change the neural connections that keep individuals in chronic pain states.[56]

38% to 40% of adults living in the United States use complementary and alternative medicine therapies,[1] yet only 42% have told their primary physician that they do so.[2]

Ayahuasca, N, N-Dimethyltryptamine (DMT), lysergic acid diethylamide (LSD), psilocybin, methamphetamine (MDMA), mescaline (peyote), ketamine, and ibogaine are all subjects of ongoing research in the clinical care for the treatment of depression, addictions, and PTSD-related symptoms.[57]

Concluding Thoughts

Psychoeducation is integral to helping patients understand how their symptoms—physical, mental, emotional, and spiritual—arise from their traumatic experiences. The qualities of the clinical relationship—compassion, empathy, and rapport—are the foundation of successful trauma treatment. Next steps might include obtaining a personal consultation in integrative mental health—much as we do when we undergo psychotherapy prior to becoming a therapist—or exploring studies in integrative medicine for mental health by taking courses or attending conferences.

For those interested in learning more, additional resources can be found via the Leslie Korn Institute for Integrative Medicine, the Integrative Psychiatry Institute, Integrative Medicine for Mental Health, and Psychiatry Redefined.

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Neurobiological Mechanisms of Mind-Body Medicine

Helen Lavretsky, MD, MS; Tanya Datta

CLINICAL CASE VIGNETTE

In our post–COVID-19 clinic, we utilize mind-body practices to reduce stress of COVID-19 and long COVID–related illnesses with breath-based practices of individual choice; these include brief yogic practices, yoga classes, tai chi classes, and brief breathing exercises of 5 to 10 minutes a day using a "boxed" breath of 3-3-3-3 or 4-4-4-4 to arrive at 4 to 6 breaths per minute, which are well studied and documented to reduce blood pressure and heart rate by activating parasympathetic vagal response and reducing sympathetic overdrive.

"Ms Arnold" is a 23-year-old recent college graduate undergoing a competitive internship at a television production company who presented with complaints of brain fog, anxiety, insomnia, and headaches following 2 repeated COVID-19 infections in the past year. Among several choices of mind-body practices, she selected brief breathing practices and grounding exercises, as well as taking time to connect with nature to reduce anxiety and insomnia and help clear her mind that was now lacking "a capacity for creative thought."

She practiced on the weekends and at work when experiencing anxiety. After approximately 2 weeks, she reported a greater sense of calm and an improved ability to regulate and reduce anxiety that was also helpful in reducing both her fear of failing at her job and her insomnia. This practice provided her with a lifelong tool for self-regulation and stress-reduction techniques.

Our collective resilience has been challenged in recent years, with increased global existential crisis prompted by the COVID-19 pandemic, financial and food insecurities, global inflation, racial and political tensions, wars and the global refugee crisis, and profound climate disasters. Mental health crisis has deepened with almost a 3-fold increase in psychological distress over the past several years highlighting the vastly insufficient infrastructure that needs to fit the growing need in mental health services that is now captured by the Surgeon General advisory and the White House new policy to increase investments in mental health.[1,2] Approaches that are minimally invasive, cost-effective, culturally acceptable, and scalable are essential to the successful management of global mental health needs.

For thousands of years, ancient Eastern contemplative practices have been used by humans to expand consciousness, obtain enlightenment, and connect to one's spiritual nature, as well as to balance mental and physical health and maintain longevity. In recent times in the West, these practices have been used by millions of individuals for reducing stress, enhancing well-being, and improving coping with chronic diseases of aging. Rooted in ancient meditative traditions, mind-body practices can offer simple and scalable tools of self-regulation that incorporate controlled paced breathing (eg, yoga, tai chi, and qigong), which are therapeutic in alleviating symptoms of stress, anxiety, depression, and chronic pain disorders.[3] At the same time, the public has demonstrated a growing interest in the tools for self-regulation and acceptance of these ancient meditative practices. Recent surveys indicate roughly 15% to 19% of US adults are engaged in meditative and yoga practices. Rates among those with a mental health disorder—most commonly anxiety, stress, and depression—are even higher.[4] Yet without clear understanding of the underlying neural and physiological mechanisms, development of better treatments is difficult, especially with a goal of optimal personalized options per the National Institutes of Health Precision Medicine Initiative.

Meditative practices (eg, mindfulness-based therapies, transcendental meditation, mantra meditation, and yoga) have demonstrated efficacy for enhancing mental health in a range of clinical and healthy populations.[5] Meditative therapies confer a lower risk of adverse effects compared with more invasive approaches, have been shown to reduce adverse effects associated with pharmacological treatment,[6] and have potential to build lifelong skills with benefits far beyond initial training. Both meditative movement (eg, yoga) and multicomponent mindfulness-based interventions (eg, mindfulness-based cognitive therapy and mindfulness-based relapse prevention) appear at least as effective as other active treatments for disorders such as major depression and substance use disorder.

In healthy adults, studies suggest that multicomponent interventions such as mindfulness-based stress reduction have potential to increase empathy, self-control, self-compassion, relationship quality, and spirituality and to decrease rumination.[7] Translational neuroscience of mind-body therapies has also begun to evaluate the neurobiological mechanisms by which meditative therapies enhance resilience to mental health disorders, and several promising mechanistic domains have been identified (**Table**).

TABLE.
Neurobiological Mechanistic Domains to Enhance Resilience
- Neural
- Hormonal
- Immune
- Cellular
- Cardiorespiratory

Neurobiological Mechanisms

As a whole, meditative therapies appear effective for improving psychological well-being across a wide range of populations. However, the psychological mechanisms by which meditative therapies affect clinical outcomes are poorly understood. Broadly, meditation practice is hypothesized to increase well-being via improvement in self-regulation,[7] but significant differences in mechanisms may exist depending on the type or component of meditative therapy being used, such as chanting, pranayama, or various forms of movement (yoga, tai chi, qigong). A recent systematic review of mindfulness interventions concluded that decreases in cognitive reactivity, emotional reactivity, rumination, and worry may mediate the effect of mindfulness practice on mental health.[8] Existing research on biological mechanisms offer some support for these findings.[9] A model of the hypothesized mechanisms by which meditative therapies may increase resilience to mental illness is presented in the **Figure**.[10]

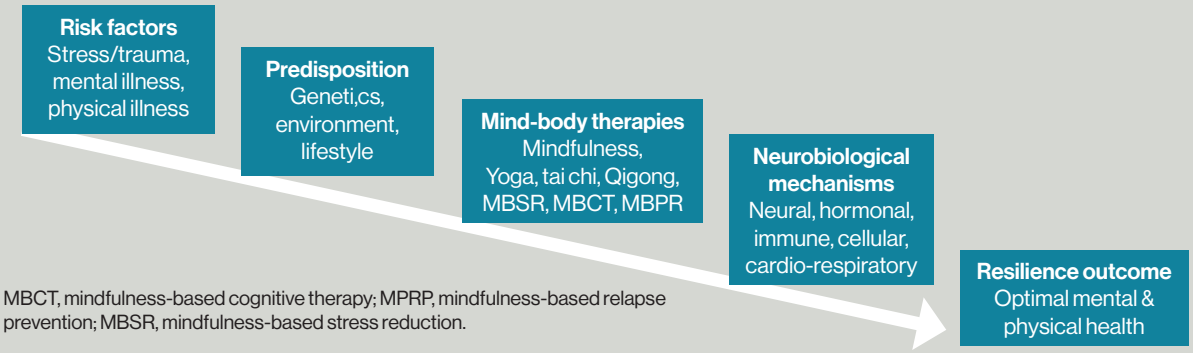
Neural Mechanisms

Neuroimaging studies suggest that mindfulness practice alters both brain structure and function. A recent meta-analysis of MRI studies used an activation likelihood estimation approach to identify brain regions that are consistently altered during meditation practice. Identified regions included those involved in processing self-relevant information (eg, precuneus); self-regulation, focused problem-solving, and adaptive behavior (anterior cingulate cortex); interoception (insula); reorienting attention (angular gyrus); and experiential self-processing (premotor cortex and superior frontal gyrus). In addition, significant structural differences were observed between expert meditators and novices, with expert meditators showing greater gray matter volume in the right anterior cingulate.[11] One possible interpretation of these data is that these neural differences are the result of long-term meditation practice and increased "brain fitness" due to training and account for the superior self-regulatory abilities observed in long-term meditators.

In our own recent studies of tai chi compared with health education plus the standard antidepressant treatment, we found that tai chi practices were associated with a much increased

resting-state brain connectivity between different parts of the brain that was also related to a reduction in depressive symptoms vs health education activity.[12] In 2 sequential studies of kundalini yoga in older adults with mild cognitive impairment and women at risk for Alzheimer disease, we found that the yoga-practicing group demonstrated increased gray matter volumes in areas of the brain related to memory and executive functioning, increased functional connectivity, and increased brain choline concentration that was related to memory performance compared with the memory training control group.[13,14]

FIGURE. A Model of Hypothesized Mechanisms by Which Meditative Therapies May Increase Resilience to Mental Illness[10]



MBCT, mindfulness-based cognitive therapy; MPRP, mindfulness-based relapse prevention; MBSR, mindfulness-based stress reduction.

Stress Response and the HPA Axis

Chronic, uncontrollable stress is a known risk factor for depression and other mental illness, and one prominent hypothesis is that chronic stress increases this risk via sustained activation and ultimate dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. Increased cortisol secretion and sustained elevated levels of cortisol eventually suppress the output of corticotropin-releasing hormone and adrenocorticotropin hormone. Once in motion, this stress-related biological cascade can be exacerbated by environmental factors (eg, social isolation, loneliness) or maladaptive coping behaviors (sedentary lifestyle, substance abuse).[15]

Several studies suggest that restoration of HPA axis dysregulation may be one mechanism by which yoga and other meditative therapies improve mental health.[16] Studies of younger healthy adults as well as sedentary community-dwelling older adults suggest that yoga may lead to both acute reductions in HPA axis activity as well as longer-term changes with repeated practice.[17] Results of several studies suggest that yoga reduces cortisol secretion (although not all studies demonstrate this effect) and increase the cortisol awakening response.[18] Some forms of meditation practice appear to reduce cortisol secretion, although there is some inconsistency of findings here as well. Larger sample sizes and use of standardized methodology will help clarify these findings.

Immune and Inflammatory Markers

Inflammation is another pathway by which stress is thought to increase risk for depression and other mental health disorders.[19] Results of a systematic review of randomized controlled trials investigating the effect of mindfulness meditation on the immune system suggest that mindfulness may affect specific markers of inflammation, cell-mediated immunity, and biological aging.[20] In recent years, multiple studies, including our own, have documented positive effects of mind-body practices on inflammatory markers, mostly via rebalancing of autonomic nervous system tone.

Cellular Protection and Repair Markers

Mind-body practices have a broad ability to reverse or slow down biological aging as claimed by the ancient yogic texts. Lavretsky and colleagues investigated the mechanisms by which the chanting meditation Kirtan Kriya reduced symptoms of depression in stressed informal caregivers of individuals with dementia.[16] Compared with listening to relaxing music, Kirtan Kriya led to significant improvements in depressive symptoms, quality of life, and telomerase activity in peripheral blood mononuclear cells (a stress-activated signal of aging). Furthermore, change in telomerase activity was correlated with depression improvement in the Kirtan Kriya group but not in the control group. These results indicate inflammatory and antiviral transcription pathways as one mechanism by which meditation may buffer against the negative effects of chronic stress on mood. Other studies have also shown that mindfulness interventions may protect against cellular aging.[21]

Brain-derived neurotrophic factor (BDNF) is an important modulator of neural development and plasticity as well as neuronal survival. Multiple studies have found a relationship between meditative practices and BDNF. For example, 1 pre/post study found increases in BDNF during a 3-month yoga and meditation retreat.[18]

Cardio-Respiratory Mechanisms

Although controlled breathing is a component of many meditative interventions, the biological mechanisms by which controlled breathing affects self-regulation and mental health remain underexplored. Existing evidence suggests that the short-term practice of yogic breathing (pranayama*)* produces a positive impact on cardiovascular and respiratory systems. Slow-paced breathing leads to reduced heart rate and blood pressure. Fast-paced breathing leads to an increase in heart rate, though less robust.[22]

Changes in heart rate variability (HRV) also support the notion that the practice of pranayama improves respiratory function and autonomic tone. HRV can represent the ability of the autonomic nervous system to adapt to a changing psychological, social, and physical environment. Thus, higher HRV is thought to reflect a greater capacity for self-regulation. In neuroimaging studies of both younger and older adults, higher HRV is associated with higher resting-state functional connectivity between the medial prefrontal cortex and amygdala (a biomarker of emotion regulation), with resilience to the development of mental health disorders.[23] Multiple studies have linked meditative practices to indicators of increased parasympathetic activity compared with other kinds of exercises. For example, research with pregnant women suggests that yoga has potential to increase the high-frequency band of the HRV spectrum during meditation (an indicator of parasympathetic activity) compared with standard prenatal exercises.[24]

It has been hypothesized that the effects of pranayama are mediated by the vagal nerve system through interconnections between the peripheral sensory organs, solitary nucleus, thalamus, amygdala, limbic areas, and prefrontal cortex.[25] Research suggests that the increase of parasympathetic activity associated with increased expiration time reduces the release of stress hormones, reduces amygdala activation via enhanced γ-aminobutyric acid inhibition from the prefrontal cortex and insula, and reduces psychological and somatic symptoms associated with stress.[26]

Translational research on the effects of pranayama on the neural networks involved in respiratory control, breath awareness, interoception, and emotion regulation is still in its infancy. Our group is working to develop rodent and human models of respiratory control of emotion regulation in anxiety and panic. This represents a translational model of breath-based, mind-body interventions focused on the mechanisms by which controlled breathing in pranayama can affect emotions and resilience.

Technological Innovation

Interest in scalable health solutions has grown exponentially during the COVID-19 pandemic. Digital behavioral health inventions, such as meditation and mobile apps for health, are frequently cited as cost-effective methods that can overcome face-to-face delivery barriers such as cost, stigma, and access to health care providers, particularly when they can be self-administered by the patient.[27]

A 2017 meta-analysis of randomized controlled trials testing the efficacy of mental health apps for depression identified 6 apps that included a

mindfulness component, which had a significant medium-sized effect on reducing depressive symptoms similar to cognitive behavioral therapy–based apps. Additionally, virtual reality interventions reported increases in mindfulness and relaxation and decreases in sadness, anger, and anxiety.[28]

Directions for Future Research

Current models of mental health service delivery fail to adequately address the enormous burden of mental health disorders worldwide. Existing evidence suggests that mind-body therapies have potential to improve mental health in a variety of populations. Effects appear largest among individuals with psychological disorders, although benefits have also been observed in healthy adults as well as those with physical health conditions. Further research is needed to determine which types of interventions are most effective for which disorders and outcomes, identify the active ingredients of interventions, and determine the biological processes that mediate observed effects. Work in each of these areas will inform the development of more potent and individualized interventions to fulfill the mandate of precision medicine.

In addition, studies investigating the cost-effectiveness of implementing mind-body therapies for primary or secondary prevention of chronic physical and mental disorders will be important for informing public health policies and may facilitate the integration of such therapies into mainstream Western medicine health care. Transdisciplinary "precision medicine" approaches that combine studies of basic neurobiology of breathing in animal and human models of stress can help characterize physiological and neural biomarkers and mechanisms of breathing control and emotion regulation in humans.[29] Such mechanistic research is fundamental for the development of more effective and mechanism-based mind-body therapies for stress-related disorders. Mind-body interventions like tai chi and other breath-related practices can also be used to help improve COVID-19 and long COVID–related symptoms.[30]

Dr Lavretsky is a professor in residence in the Department of Psychiatry at UCLA in Los Angeles, California. Her work on geriatric depression and integrative mental health using mind-body interventions has received national attention, and she has won numerous grants supporting that work. She is the president-elect of the American Association for Geriatric Psychiatry, a distinguished fellow of the American Psychiatric Association and of the American Association for Geriatric Psychiatry, and a fellow of the American College of Neuropsychopharmacology. She is also on the board of *Psychiatric Times*™. **Ms Datta** is a fourth-year medical student at the David Geffen School of Medicine at UCLA. She studied behavioral neuroscience at the University of Pennsylvania as an undergraduate student. She is currently applying for residency in psychiatry and is interested in pursuing a career in integrative mental health.

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Herbal Medicine
What You Need to Know

Beata Bliss Lewis, MD

Herbal medicines have been used to treat mental health disorders since ancient times. Many of the medications used in contemporary medicine originated from plants—salicylic acid from the willow tree, for example, and morphine from poppies. Numerous botanical treatments are useful in general psychiatry. Although there are many herbal medicines, this article discusses the ones most commonly used to treat mental health concerns (**Table 1**).

Americans spent $11.3 billion on herbal supplements in 2020, which represented a record increase in spending of 17.3% from 2019 to 2020.[1] According to the 2020 COVID-19 consumer survey of the Council for Responsible Nutrition,[2] among those who increased supplement intake, nearly a quarter cited mental health-related reasons, including stress and anxiety.[3]

US consumers are spending the most money on the following herbs with mental health applications: cannabidiol (CBD), ashwagandha (*Withania somnifera*), turmeric, gingko, St. John's wort (SJW), valerian, maca, and rhodiola. Several of these herbs also have applications for physical health, such as inflammation, cardiovascular disease, and physical performance.

Unfortunately, the research evidence and consumer spending do not align. As psychiatrists, we can help guide our patients in making beneficial choices when they choose to take herbs.

Most of the psychotropic herbal medicines available over the counter are quite safe, with fewer adverse effects than conventional antidepressants or antianxiety agents.[4] Yet not all are safe. For example, SJW could cause a switch to mania in bipolar disorder[5]; also, it should not be taken with certain other drugs due to potential interactions.[6] Kava supplements made from the incorrect plant type and incorrectly processed have caused liver toxicity.[7] Thus, it is important to know which herbal agents your patient may be taking and whether herbal medications may be interact-

TABLE 1. Most Commonly Used Herbal Medicines

Herb	Indications	Dose	Adverse effects	Evidence level
St. John's wort	Mild-to-moderate depression	300 mg-1800 mg per day	**Mild:** dermatological and gastrointestinal issues **Severe:** potential switch to mania in bipolar disorder, serotonin syndrome, drug-drug interactions	**Good:** multiple positive meta-analyses, including positive Cochrane meta-analysis of 5489 adults, and a 2016 review of 35 studies and 7000 patients
Turmeric	Depression, anxiety, depression with inflammation; antioxidant, neuroprotective and monoamine regulatory effects	1000 mg per day with 10 mg piperine	In most research studies, none reported	**Moderate:** 2020 positive meta-analysis of 10 studies of 570 patients, second smaller meta-analysis positive for depression
Saffron	Depression, anxiety, insomnia	50 mg per day	Generally safe; may be of concern in those with low blood pressure, low blood counts, or coagulation disorders	Low
Lavender	Depression, anxiety	Silexan 80 mg per day	Eructation	Low
Cannabidiol	Anxiety, sleep, inflammation	5 mg-45 mg	Well tolerated at low dose. At higher dose: drug-drug interactions, hepatic abnormalities, diarrhea, fatigue, vomiting, somnolence	Low

ing with conventional medications.

Herbal medicines are more complex than conventional medications, which may discourage psychiatrists from recommending them. Take heart: Most herbs are quite safe. It may be easiest to select 2 or 3 herbs, to start, and learn about them in depth. Alternately, choose to learn about the herbs your patients are already using and mixing with the conventional medications we may be prescribing.

Herbs' complexity comes from the fact that they are whole plants rather than a single chemical active ingredient in a medication. A plant's beneficial effect may be related to complex synergistic and polyvalent interactions among many of its own components or multiple plants. A plant or herbal combination may contain multiple molecules with different physiological effects, or it may modify the absorption or metabolism of other bioactive components, or it may reduce adverse effects. For example, adding black pepper to turmeric may dramatically enhance the absorption of turmeric into the bloodstream.[8] Within a single plant, valerian has several different effects including anxiolysis, muscle relaxation, and sleep promotion; notably, valerian involves a number of compounds such as free GABA; benzodiazepine receptor-binding flavonoids; terpenes, which inhibit GABA breakdown and cause smooth muscle relaxation; and lignans, which inhibit serotonin binding.

Herbal medicines may work better because of the complex and synergistic interactions, yet that strength is an obstacle to standardized research, and it may worry clinicians. Comparing the results of studies on different preparations of the same herb produced by different manufacturers may be difficult. The exact chemical composition of an herbal preparation is dependent on many factors, described in **Table 2**.

TABLE 2. Factors That Determine the Exact Chemical Composition of an Herbal Preparation

- Genetic differences resulting in different phytochemicals
- Environmental differences related to climate, temperature, rain, etc
- Soil quality
- Exposure to pests
- Differences in plant parts used (eg, root, bark, leaf)
- Harvest time
- Preparation method

TABLE 3. Key Mechanisms of Action of Herbal Medicines Identified in Research

1. Modulation of neuronal communication via plant components binding to neurotransmitter receptors
2. Alteration of neurotransmitter synthesis and function
3. Stimulating or sedating central nervous system activity
4. Regulating endocrine system (eg, lowering cortisol secretion)
5. Epigenetic changes and regulating gene expression
6. Lowering inflammation
7. Reducing oxidative stress
8. Modulating brain-derived neurotrophic factor and other relevant pathways
9. Modulation of opioid and cannabinoid systems

Research on herbal medicines is elucidating the mental health effects and underlying mechanisms of action of many individual herbs, a few of which are discussed in this article. Herbal medicines may have antidepressant, anxiolytic, sedative, hypnotic, analgesic, and cognitive-enhancing effects, in addition to "adaptogenic" effects, that increase resilience to stress. Key mechanisms of actions of herbal medicines identified in research can be found in **Table 3**.

Concluding Thoughts

Herbal medicine is an important addition to our conventional medication toolbox. Herbs are generally well tolerated and affordable. For patients interested in using herbs, we have sufficient evidence to recommend several agents discussed in this article. It is important to ask patients what herbs and supplements they take and to assess for potential drug-herb interactions and adverse effects.

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Bipolar Update

Lithium and Suicide Prevention

More Thoughts on Recent VA Study

David N. Osser, MD

There has been much discussion of the recently published large (519 participants) US Department of Veterans Affairs (VA)–sponsored randomized clinical trial of lithium versus placebo to prevent suicide attempts, hospitalizations to prevent suicide, and deaths after a previous attempt.[1] The distinguished group of investigators found no advantage for lithium, and the study was actually interrupted earlier than planned because of the negative results on preliminary analysis. The authors concluded that "simply" adding lithium to existing medication regimens is unlikely to be effective in preventing a broad range of suicide-related events. An editorial by Baldessarini and Tondo, however, proposed instead that the findings "cannot be taken as evidence that lithium lacks antisuicidal effects" due to numerous serious limitations in the study.[2]

The first of those limitations was that most patients had nonbipolar depression (only 15% had bipolar I or II disorder), a heterogeneous population for which the antisuicidal effects of lithium are perhaps less established. Additionally, the lithium level, which was low overall (0.54 mEq/L), was particularly low in the patients with nonbipolar depression (0.46 mEq/L). Notably, an important previous study (the LiTMUS trial) found no value in general to adding a similar "moderate" dose of lithium for 6 months in patients with bipolar disorder[3]—so the dose issue could be critical. Length of time on treatment was not much longer in the latest trial: 38 weeks. In significant recent support of lithium, a systematic review (not cited in the study or the editorial) evaluated studies involving more than 200,000 participants pertinent to the question of suicide prevention, including patients with mood disorder and others, and concluded that lithium was associated with a significant reduction in suicide behaviors.[4]

Another flaw noted by Baldessarini and Tondo was the large dropout rate of 52%, many of them early in the study. This quantity of dropouts would make any study hard to interpret.

The study was also problematic in having a lot of important comorbidities in the participants. Substance use was present in 85%. This would be likely to reduce the impact of any bipolar treatments applied and is a large factor in suicidal behaviors. It is also very likely to reduce the potential for finding a difference between lithium and placebo. Other conditions associated with suicide (matched in the lithium and control groups as best as possible) were present in large numbers including personality, anxiety, and other

disorders—and these would also tend to reduce drug-placebo differences.

Furthermore, the editorial notes that there was no analysis of what other medications the patients were on that might have reduced lithium effectiveness. Antidepressants come to mind because they are often included in the regimens of patients with bipolar disorder, and this use is potentially harmful according to some evidence. For example, the STEP-BD study found that inclusion of an antidepressant in the regimen of rapid-cycling patients with bipolar disorder tripled the rate of recurring depression compared with not taking an antidepressant, even if the patient was on a mood stabilizer.[5]

The study was not totally negative with respect to lithium's potential benefits for patients with bipolar disorder. In the small number (N = 30) of patients with bipolar disorder in the study for which the primary outcomes were available (first and subsequent suicide-related events), there were 10 events in the lithium group and 20 in the placebo group.[1] This was not statistically significant due to the small N, but numerically it is rather impressive in favor of lithium.

In conclusion, despite this new study and the need for further research, the best recommendation at this time regarding lithium in patients with bipolar disorder who are suicidal would be to consider it a worthwhile option. However, it would be important to prioritize treating comorbid substance use disorders and other comorbidities that could affect suicide before—or at least at the same time as—adding lithium to address suicidal thoughts and behaviors. One should not "simply" add lithium.

After adding lithium, if the patient is on an antidepressant, it is advisable to taper off the antide-

pressant(s). If needed due to persisting or recurrent depression, consider adding evidence-based bipolar depression medications such as lamotrigine, lurasidone, quetiapine, or cariprazine.[6] Lumateperone received US Food and Drug Administration (FDA) approval for bipolar depression in December 2021, so that could be considered as well.[7] According to a news release, there have been 2 other unpublished lumateperone studies, with one showing no efficacy and the other showing that using lumateperone as an adjunct to lithium or valproate had a small benefit.

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

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

Important Safety Information

Boxed Warnings:

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. CAPLYTA is not approved for the treatment of patients with dementia-related psychosis.**
- **Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric and young adults in short-term studies. Closely monitor all antidepressant-treated patients for clinical worsening, and for emergence of suicidal thoughts and behaviors. The safety and effectiveness of CAPLYTA have not been established in pediatric patients.**

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

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

- **Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis,** including stroke and transient ischemic attack. See **Boxed Warning** to the left.
- **Neuroleptic Malignant Syndrome,** which is a potentially fatal reaction. Signs and symptoms include hyperpyrexia, muscle rigidity, delirium, autonomic instability, elevated creatinine phosphokinase, myoglobinuria (and/or rhabdomyolysis), and acute renal failure. Manage with immediate discontinuation of CAPLYTA and provide intensive symptomatic treatment and monitoring.
- **Tardive Dyskinesia (TD),** a syndrome of potentially irreversible, dyskinetic, and involuntary movements which may increase as the duration of treatment and total cumulative dose increases. The syndrome can develop after a relatively brief treatment period, even at low doses, or after treatment discontinuation. Given these considerations, CAPLYTA should be prescribed in a manner most likely to reduce the risk of TD. Discontinue CAPLYTA if clinically appropriate.
- **Metabolic Changes,** including hyperglycemia, diabetes mellitus, dyslipidemia, and weight gain. Hyperglycemia, in some cases extreme and associated with ketoacidosis, hyperosmolar coma or death, has been reported in patients treated with antipsychotics. Measure weight and assess fasting plasma glucose and lipids when initiating CAPLYTA and monitor periodically during long-term treatment.

Help your patients get relief from their bipolar depression with titration-free, once-daily CAPLYTA 42 mg

Choose CAPLYTA

for a broad range of adults with bipolar depression[1]

- Proven efficacy in bipolar depression (bipolar I & II)*
- Once-daily, titration-free dosing—patients start on the effective dose
- Broad access
- Changes in weight and akathisia were similar to placebo at week 6[1]
  - Antipsychotic drugs have been reported to cause metabolic effects and tardive dyskinesia
    Please see Important Safety Information below.

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

- **Leukopenia, Neutropenia, and Agranulocytosis (including fatal cases).** Perform complete blood counts in patients with pre-existing low white blood cell count (WBC) or history of leukopenia or neutropenia. Discontinue CAPLYTA if clinically significant decline in WBC occurs in absence of other causative factors.
- **Orthostatic Hypotension and Syncope.** Monitor heart rate and blood pressure and warn patients with known cardiovascular or cerebrovascular disease. Orthostatic vital signs should be monitored in patients who are vulnerable to hypotension.
- **Falls.** CAPLYTA may cause somnolence, postural hypotension, and motor and/or sensory instability, which may lead to falls and, consequently, fractures and other injuries. Assess patients for risk when using CAPLYTA.
- **Seizures.** Use CAPLYTA cautiously in patients with a history of seizures or with conditions that lower seizure threshold.
- **Potential for Cognitive and Motor Impairment.** Advise patients to use caution when operating machinery or motor vehicles until they know how CAPLYTA affects them.
- **Body Temperature Dysregulation.** Use CAPLYTA with caution in patients who may experience conditions that may increase core body temperature such as strenuous exercise, extreme heat, dehydration, or concomitant anticholinergics.
- **Dysphagia.** Use CAPLYTA with caution in patients at risk for aspiration.

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

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

Adverse Reactions: The most common adverse reactions in clinical trials with CAPLYTA vs placebo were:

- Schizophrenia: somnolence/sedation (24% vs 10%) and dry mouth (6% vs 2%).
- Bipolar Depression (Monotherapy, Adjunctive therapy): somnolence/sedation (13% vs 3%, 13% vs 3%), dizziness (8% vs 4%, 11% vs 2%), nausea (8% vs 3%, 9% vs 4%), and dry mouth (5% vs 1%, 5% vs 1%).

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

References: 1. CAPLYTA prescribing information, 2021.

CAPLYTA®
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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; and SUICIDAL THOUGHTS AND BEHAVIORS

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.

Suicidal Thoughts and Behaviors

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

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

Recommended Dosage: The recommended dosage of CAPLYTA is 42 mg administered orally once daily with or without food. Dose titration is not required.

Dosage Recommendations for Concomitant Use with CYP3A4 Inducers and Moderate or Strong CYP3A4 Inhibitors: Coadministration with CYP3A4 Inducers - Avoid concomitant use of CAPLYTA with CYP3A4 inducers. Coadministration with Moderate or Strong CYP3A4 Inhibitors - Avoid concomitant use of CAPLYTA with moderate or strong CYP3A4 inhibitors.

Dosage Recommendations for Patients with Hepatic Impairment: Avoid use of CAPLYTA in patients with moderate or severe hepatic impairment (Child-Pugh B or C).

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.

Suicidal Thoughts and Behaviors in Children, Adolescents and Young Adults: In pooled analyses of placebo-controlled trials of antidepressant drugs (SSRIs and other antidepressant classes) that included approximately 77,000 adult patients and 4,500 pediatric patients, the incidence of suicidal thoughts and behaviors in antidepressant-treated patients age 24 years and younger was greater than in placebo-treated patients. There was considerable variation in risk of suicidal thoughts and behaviors among drugs, but there was an increased risk identified in young patients for most drugs studied. There were differences in absolute risk of suicidal thoughts and behaviors across the different indications, with the highest incidence in patients with MDD. The risk differences (drug-placebo difference) in the number of cases of suicidal thoughts and behaviors in the pooled placebo-controlled trials of antidepressants in pediatric* and adult patients per 1000 patients treated are as follows: ***Increases Compared to Placebo*** – <18 years old: 14 additional patients; 18-24 years old: 5 additional patients. ***Decreases Compared to Placebo*** – 25-64 years old: 1 fewer patient; >65 years old: 6 fewer patients. *CAPLYTA is not approved for use in pediatric patients.

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

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

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 antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, delirium, and autonomic instability. Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. If NMS is suspected, immediately discontinue CAPLYTA and provide intensive symptomatic treatment and monitoring.

Tardive Dyskinesia: Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with antipsychotic drugs. The risk 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.

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

In an uncontrolled open-label trial of CAPLYTA for up to 1 year in patients with stable schizophrenia, the percentages of patients with 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.

Bipolar Depression - In data from short-term (6-week), placebo-controlled monotherapy and adjunctive therapy bipolar depression trials, mean changes from baseline and the proportion of patients with shifts from normal to greater than normal levels of fasting glucose and insulin in patients treated with CAPLYTA were similar to those in patients treated with placebo.

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.

Schizophrenia - In pooled data from short-term (4- to 6-week), placebo-controlled trials of adult patients with schizophrenia, mean changes from baseline and the proportion of patients with shifts 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.

Bipolar Depression - In data from short-term (6-week), placebo-controlled monotherapy and adjunctive therapy bipolar depression trials, mean changes from baseline and the proportion of patients with shifts to higher levels of fasting total cholesterol and triglycerides were similar in patients treated with CAPLYTA and placebo.

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

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

Schizophrenia - 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.

Bipolar Depression - In data from short-term (6-week), placebo-controlled monotherapy and adjunctive therapy bipolar depression trials, mean changes from baseline and the proportion of patients with an increase in weight ≥7% from baseline to end of study were similar in patients treated with CAPLYTA and placebo.

In an uncontrolled open-label trial of CAPLYTA for up to 6 months in patients with bipolar depression, the mean change in body weight was -0.01 kg (SD 3.1) at Day 175.

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/mm^3 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. 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.

Schizophrenia - In pooled data from short-term (4- to 6-week), placebo-controlled schizophrenia 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%.

Bipolar Depression - In data from short-term (6-week), placebo-controlled monotherapy and adjunctive therapy bipolar depression trials, the frequencies of orthostatic hypotension for CAPLYTA and placebo were both 0%. The rates of syncope for CAPLYTA and placebo were 0.3% and 0.5%, respectively in the monotherapy trials, and there were no reports for CAPLYTA or placebo in the adjunctive therapy trial.

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. 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.

Schizophrenia - 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.

Bipolar Depression - In short term (6-week), placebo-controlled monotherapy and adjunctive therapy bipolar depression clinical trials, somnolence and sedation were reported in 13% of CAPLYTA-treated patients, compared to 3% of placebo-treated patients.

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

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

The safety of CAPLYTA has been evaluated in placebo-controlled clinical trials in 2664 adult patients with schizophrenia and bipolar depression exposed to one or more doses. A total of 402 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.

Schizophrenia - 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).

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) were as follows (*adverse reaction is followed by percentage of patients treated with CAPLYTA 42 mg (n=406) and patients treated with placebo (n=412) in parentheses*): Somnolence/ Sedation (24%, 10%); Nausea (9%, 5%); Dry Mouth (6%, 2%); Dizziness[1] (5%, 3%); Creatine Phosphokinase Increased (4%, 1%); Fatigue (3%, 1%); Vomiting (3%, 2%); Hepatic Transaminases Increased[2] (2%, 1%); Decreased Appetite (2%, 1%). [1]Dizziness, dizziness postural; [2] ALT, AST, "hepatic enzymes" increased, or liver function test abnormal.

Bipolar Depression – Monotherapy

The following findings are based on the pooled short-term (6-week), placebo-controlled monotherapy bipolar depression studies in adult patients treated with CAPLYTA administered at a daily dose of 42 mg (N=372).

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, dizziness, nausea, and dry mouth.

Adverse reactions associated with CAPLYTA (incidence of at least 2% in patients exposed to CAPLYTA and greater than placebo) were as follows (*adverse reaction is followed by percentage of patients treated with CAPLYTA 42 mg (n=372) and patients treated with placebo (n=374) in parentheses*): Headache (14%, 8%); Somnolence/Sedation (13%, 3%); Dizziness[1] (8%, 4%); Nausea (8%, 3%); Dry Mouth (5%, 1%); Diarrhea (4%, 2%); Vomiting (4%, 0%); Abdominal pain[2] (2%, 1%); Upper respiratory tract infection (2%, 1%). [1]Dizziness, dizziness postural; [2]Abdominal discomfort, abdominal pain, abdominal pain upper and lower.

Bipolar Depression - Adjunctive Therapy with Lithium or Valproate - The following findings are based on a 6-week, placebo-controlled adjunctive therapy bipolar depression study in adult patients treated with CAPLYTA administered at a daily dose of 42 mg (N=177).

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, dizziness, nausea, and dry mouth.

Adverse reactions associated with CAPLYTA (incidence of at least 2% in patients exposed to CAPLYTA and greater than placebo) were as follows (*adverse reaction is followed by percentage of patients treated with CAPLYTA 42 mg (n=177) and patients treated with placebo (n=175) in parentheses*): Somnolence/ Sedation (13%, 3%); Dizziness[1] (11%, 2%); Nausea (9%, 4%); Dry Mouth (5%, 1%); Vomiting (4%, 0%), Diarrhea (3%, 2%); Upper respiratory tract infection (3%, 1%); Blurred vision (3%, 1%), Increased blood prolactin (2%, 0%). [1]Dizziness, dizziness postural.

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 (EPS) - In the short-term, placebo-controlled schizophrenia and bipolar depression studies, data was objectively collected on 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).

Schizophrenia - In the 4- to 6-week, placebo-controlled schizophrenia 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 schizophrenia trials, 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.

Bipolar Depression - In the 6-week, monotherapy bipolar depression trials, the frequency of reported reactions related to EPS, including muscle spasms, dyskinesia, extrapyramidal disorder, movement disorder, tremor, restlessness, and akathisia was 1.3% for CAPLYTA and 1.1% for placebo.

In a 6-week, adjunctive therapy bipolar depression trial, the frequency of reported reactions related to EPS, including tremor, muscle spasms, akathisia, extrapyramidal disorder, gait disturbance, and restlessness was 4.0% for CAPLYTA and 2.3% for placebo.

In the 6-week, monotherapy bipolar depression trials, the mean changes from baseline for CAPLYTA-treated patients and placebo-treated patients were 0 and 0 for the SAS, -0.1 and -0.1 for the BARS, and 0 and 0 for the AIMS, respectively. In the 6-week adjunctive therapy bipolar depression trial, the mean changes from baseline for CAPLYTA-treated patients and placebo-treated patients were 0 and 0 for the SAS, 0 and -0.1 for the BARS, and 0 and 0 for the AIMS, respectively.

DRUG INTERACTIONS

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.

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 *(see Clinical Considerations).* 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 *(see Clinical Considerations).* 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/m^2 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 *(see Data).*

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/m^2 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/m^2 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/m^2 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. Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric patients.

Geriatric Use: Controlled clinical studies of CAPLYTA in the treatment of schizophrenia did not include any patients aged 65 or older to determine whether or not they respond differently from younger patients. Controlled clinical studies of CAPLYTA in the treatment of bipolar depression included patients aged 65 or older; the number of patients was not sufficient 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.

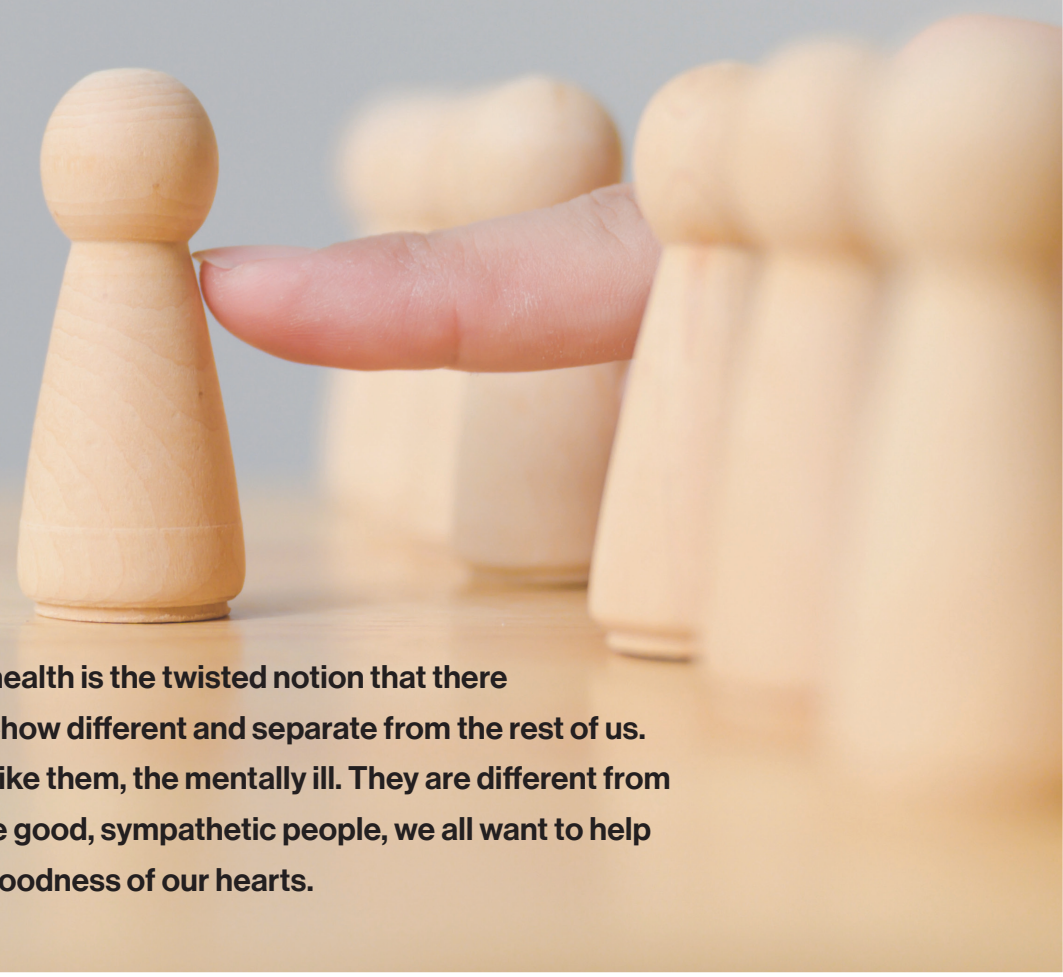
No dosage adjustment is recommended for patients with mild hepatic impairment (Child-Pugh A).

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).

Intra-Cellular THERAPIES

AFFIRMING PSYCHIATRY



Mental Health's Most Toxic Myth

Daniel Morehead, MD

The biggest and most deeply destructive myth of mental health is the twisted notion that there is a group of people called the "mentally ill" who are somehow different and separate from the rest of us. "We," the majority composed of "normal" people, are not like them, the mentally ill. They are different from the rest of us, worthy of pity and curiosity. But since we are good, sympathetic people, we all want to help "those people" who suffer from such illnesses out of the goodness of our hearts.

What is wrong with all of this? The delusional idea that we are separate in any way from the mentally ill. In fact, there is no *them* because the people who deal with mental illness are *us*. All of us. Literally all of us deal with mental illness. Every single one of us does. How can this be true? Because massive, carefully performed studies tell us that half of our population experiences some form of mental illness over the course of their lives. Fifty percent of us experience mental illness directly.[1] And what about the other 50% of us? The other 50% have the experience of seeing someone we love suffer from mental illness. Whether it is a friend, a family member, or a close coworker, every single one of us loves someone who experiences mental illness. All of us are affected by mental illness, directly or indirectly. There is no *them*; we are them.

The Myth in Psychiatry

There is no social group that does not include individuals with mental illness. Politicians, attorneys, CEOs, teachers, members of the media, and working individuals everywhere experience mental illness. There is no line we can draw anywhere in society that has individuals with mental illness on one side and individuals without it on the other. This is just as true among doctors and mental health professionals as any other group. Even in a mental health clinic or psychiatric hospital, no such line of division exists. Many of the patients are medical and mental health professionals, while many of the mental health professionals treating them experience mental illness.

How do we know this? In truth, we only have a vague idea of how many psychiatrists and other mental health professionals experience mental illness. But even the limited data we have tell us that mental illness is at least as common among our profession as it is in the rest of the population, and that it is quite likely to be higher.[2] Seventy percent of us have experienced mental illness at some point, according to available surveys.[3,4] Even more of us have a family member who has experienced mental illness. Why, after all, would most of us want to go into the field if we had no personal stake in it? According to the studies, many of us learned as children to be mediators and junior therapists in our own families who experienced the effects of mental illness.[5,6] Why, in the end, do we find our field so fascinating? Because, of course, it applies to us and to those we love. We as medical and mental health professionals deal with mental illness, and it is time for us to openly admit it.

Ending the Myth in the Office

What am I proposing? That all of us who are mental health professionals go on an internet orgy of self-revelation, parading our illnesses and private lives in the most dramatic way possible? Hardly. We have learned the hard way, individually and institutionally, that the mental health treatment we deliver is not about us. Healthy boundaries require us to avoid talking about ourselves with patients. Even if I happen to share the same illness or life trauma, I cannot fall into the trap of equating my experience of, say, anxiety or abuse, with my patient's experience of anxiety or abuse. We use every bit of our own experience to empathize, but explicitly putting our own experience into the mix of the treatment relationship only serves to confuse both clinician and patient.

What if the psychiatrist's public face changed from that of a distant prescriber to one of a fellow warrior in the trenches?

On the other hand, I am proposing that all of us become especially vigilant against any subtle implication that our patients are somehow different, separate, or inferior. They are not, and they are certainly not inferior to us. They are fellow human beings who are equally subject to illness, both mental and physical, as us. Personally, I as a clinician seek out every

opportunity to dispel the twisted notion that I and other "successful" people do not have the same struggles, problems, and vulnerability to illness as patients.

For instance, consider this bit of dialogue:

Patient: I just wish I was normal and that I did not have to take this medicine.

Psychiatrist: Is that right? Normal people don't get sick? Normal people don't take medicines? That's a pretty high standard you've got there. I'm not sure if the rest of us can live up to it.

Or this:

Patient: I don't know if you have ever felt overwhelmed by life, but no matter how hard I try, I just cannot keep up.

Psychiatrist (smiling sympathetically): No, I have never in my life felt overwhelmed or overstressed. I have no idea what that is like. Please do explain!

Let me hasten to add, I do not make these sorts of comments flippantly. In these cases, I am talking to patients I have known for years. We have had many discussions about the biological realities of mental illness, about the toxic nature of stigma, and about how common, indeed, universal it is to have some close experience to mental illness. There is a deep context to such comments. Furthermore, we always take pains to return to the shame, anxiety, and grief that the patient is revealing at the beginning of such discussions. But what we do not do in our treatment is accept pernicious and ignorant assumptions about mental health that play into stigma and inferiority.

Myth Outside of the Office

Outside the office, there are bigger changes that I would dearly love to see. What if the psychiatrist's public face changed from that of a distant prescriber to one of a fellow warrior in the trenches? The trenches, after all, are where most of us find ourselves, both personally and professionally. We fight mental illness. We suffer with our patients, our families, and with our own illnesses. Maybe we can think about new ways of presenting ourselves this way as an organized group, in our national, state, and local associations.

On an individual level, I am not proposing a performative flood of social media revelations. I am proposing quite the opposite: Rather than taking public professions of mental illness as dramatic, we take them as unexceptional. Rather than putting ourselves out there as brave risk takers, we matter-of-factly admit that we too are human and suffer from mental illness. This is not shocking. It is not dramatic. It is as "normal" as having any illness can be.

Like it or not, more of us will have to publicly discuss our mental illness to change the common perception of psychiatrists and to give us a different kind of public platform from which to end stigma. A good bit of experience with advocacy tells me that most individuals have some respect for us as physicians and even psychiatrists. But exclusively presenting ourselves as experts does not have nearly the same impact as referencing our own personal experience with mental illness. Rightly or wrongly, there is no authority today like the authority of lived experience and most of us have that authority, either as a family member or as a person with mental illness. It is time to make use of it. Only when we stand up as individuals who personally deal with mental illness will the public pay attention to us as experts who offer the decisive knowledge they need to deal with it themselves.

The Myth in the General Public

It is critical for mental health professionals to own their personal stake in mental illness as a group. But it is even more important that we use this position to help the general public do the same. Why? Because no matter how altruistic I am, if mental illness is really someone else's problem and not my problem, then I will never have the same sense of urgency and motivation to do something about it. If mental illness is someone else's problem, I will turn away from the suffering and eccentricity of those disabled by severe mental illness. I will want to live near someone with severe mental illness, and I will not want to sacrifice to help pay for the care of those with mental illness. The needs of "those people" will never be as pressing as the needs of "us people."

A vast majority of the general public, according to the polls, thinks that mental illness is real medical illness.[7] Everyone supports treatment for mental illness. Everyone says it is important. And yet we have people with mental illness literally lying in the streets because our society does not fund their treatment. We have individuals whose lives would profoundly benefit from inpatient and residential treatment who cannot get it. We have people with serious and even disabling levels of mental illness who cannot access the most effective medications or intensive forms of psychotherapy because of insurance limitations. We have people dying from under-treatment through suicide and the long-term ravages of these illnesses. In such a wealthy nation, how can this be tolerated?

If each of us truly realized and truly believed that mental illness was our own personal problem, we would not stand for this as a nation and a culture. We do not put up with severe cancer sufferers being reduced to poverty and homelessness because of inadequate treatment. If we regarded mental illness in the same way, we would not underfund our mental hospitals to the point of reducing them to near slums. We would not accept the unconscionable manipulations of insurance companies to avoid paying for adequate treatment or the well-meant but inept gestures of our governments in answer to the mental health crisis.

Concluding Thoughts

I suffer from mental illness. I have family members and close friends who suffer from mental illness. This does not make me special, and—given that I am a psychiatrist—the fact that I can publicly say so does not make me especially brave. I do not blame many of my colleagues for keeping such information about their own mental health private. Everyone has a right to keep their medical information private.

However, But in the interests of truly ending stigma and undertreatment, more of us are going to have to speak up. Even if we do not publicly identify ourselves as having mental illness, all of us need to shed the last vestiges of stigma from our own minds. And this includes never, ever regarding people with mental illness as "those people" again.

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BOOK REVIEW

Important Lessons for Psychiatry and Beyond

***Healing : Our Path From Mental Illness to Mental Health* by Thomas Insel, MD**
Penguin Press, 2022; 306 pages

Reviewed by Renato D. Alarcón, MD, MPH

AUTHOR'S NOTE: All directly quoted phrases throughout the review belong to the book's text.

A complex and fascinating process in the mental health field is the nearly unanimous recognition of a parallel advancement of sociocultural and biological knowledge components in clinical, therapeutic, diagnostic, and etiopathogenic areas. The best evidence of the resulting paradox—scientific progress and an increasing prevalence of mental illness and suffering—are documents written by individuals close to its occurrence, witnesses of an ongoing contradiction. Such is the case in *Healing: Our Path From Mental Illness to Mental Health* by Thomas Insel, MD, former National Institute of Mental Health (NIMH) director. Based on his experiences and reflections after retirement, the book is a profound and sincere recognition of his own and the US health system's misunderstanding of "the problem," as well as an embrace of "a promise" of better times amid climbing psychopathology statistics, focused on "relieving symptoms and not on helping people recover." In such context, *Healing* is both a denunciation and a redemption—a self-reproach and a request.

The introduction is a telling summary of the story evolving in the 3 parts and 12 chapters. Serious mental illness configures what Insel calls "an American tragedy" and summarizes as "simply a crisis of care." Yet the realities we know delineate a situation that is far from "simple." The crisis of care, then, "is not just lack of access but lack of engagement" on the side of patients, families, and even professionals with a variety of "attitudinal barriers." I would include here the search for "quick solutions" (ie, pills) dispensed by psychiatrists who, overwhelmed by heavy schedules and persuaded by the active publicity of the pharmaceutical industry and the ambiguous encouragement of a predominantly biological research community, devote no more than 15 minutes to each patient and choose not to talk with patients about relevant family and interpersonal issues.

Historical pieces and well-known names clearly delineate another purpose of the book: to discuss how the different perspectives are guided by political beliefs. Between the 1960s and '70s, Presidents John F. Kennedy, Lyndon B. Johnson, and James E. Carter worked to increase the federal government's involvement in providing care; in the '80s, however, President Ronald Reagan slashed federal spending, with the community mental health centers "among the first on the chopping block." Insel's consideration of the impact of his biological school of thought on psychiatric research makes him admit that "we still understand very little about how the brain works." Nevertheless, he mentions medications as the first of 4 broad treatment categories to be applied "early in the course of the disease"; the other 3 are psychological therapies, neurotherapeutics, and rehabilitative services. It is encouraging to see rehabilitative treatments described as a "whole-person care" and "a chance to build or rebuild a life," which is a critical step to prevent relapses showing "long-term effects that equal or surpass the impact of the medications."

Part 2, titled "Overcoming the Barriers to Change," starts with the need to identify 4 stages of progression in the history of a mental condition (**Table**). There is an absence of treatment for the millions who cannot be identified during the first 2 stages, and access to inpatient care (hospitalization) "is potentially a fatal failure of the care system" for those in stage 3. The deinstitutionalization of the '80s "created a legal legacy that still today blocks funds for psychiatric hospitalization."

This results in tragic paradox: Jails and prisons become de facto mental hospitals, and state mental hospitals increasingly become de facto jails and prisons, not to count the homeless or "people with mental illness sequestered in family basements or living in the urban backwaters of cheap hotels." America has invested more in prisons than in hospitals. And the book denounces another disgrace: "The nexus of police, mental illness, and violence is fraught with issues: racism, overreaction, and even neglect."

If "quality is as much of a problem as quantity," one factor may be the "little consensus among the care providers as to how to approach even the most common forms of mental illness." That a former chief of the world's highest mental health research institution makes this statement is a sad and painful confirmation of yet another reality in American psychiatry: the divergence between the routes of science and clinical practice, and the deficiencies of what must supposedly bridge education and training in both fields for the benefit of millions. The proposed solution is "collaborative care" subjected, however, to pervasive "implementation gaps" practically blocking what Insel calls "compelling scientific evidence." We will have to agree that "anyone suffering from a mental disorder faces an inadequately trained workforce, fragmentation, and delay of services, poor medical care, and lack of measurement, which preempts accountability."

The chapter titled "Precision Medicine" opens with a justification quotation from Bertolt Brecht. A "better diagnosis" is presented as the road to better outcomes that, according to this line of thought, can only be reached through the identification of "molecular markers." Diagnosis in psychiatry and in the United States has had a name (DSM) for the past 70 years, with 5 editions and 8 versions. Labeled in the book first as a "simple taxonomy" and then as a "working dictionary," used indistinctly as "a bible" or "an encyclopedia," not to mention being "a major source of revenue," DSM "has created a common language, but much of that language has not been validated by science." The aversion toward the manual (its "pernicious impact") is distilled through several paragraphs that reject the use of symptoms, deny "symptom relief" as a valid treatment objective, and charge the labels with "creating disorders where none exist."

It is not surprising that the author proposes 2 approaches (genomics and neuroscience), neither of which "has defined the core problem"; each one "is giving us a new perspective that could create a different way of diagnosing mental illness." The sad reality is that none of the genetic/genomic variations can be considered causal—only "risk factors." Similarly, the wiring brain maps revealed by neuroimaging "is not synonymous with structure" and, ultimately, "structural studies like the MRI are not useful in the diagnosis of mental illness, probably because it is not the physical map that counts as much as the traffic between brain areas." However, "the evidence for abnormal brain circuitry is not always consistent or specific…[and]…the concept of circuits…may be an inaccurate metaphor for how the brain actually computes."

Some readers may approve, but most would feel it strange to question the need of diagnosis because "labels, precise or not, get in the way of recovery…[as]…a label on human suffering pathologizes normal variation and medicalizes

human experience." Let's not forget that diagnostic systems include not only DSM or International Classification of Diseases (ICD), but also Research Domain Criteria, the NIMH proposal that, interestingly, is not mentioned in the book, although the references are obvious. The extreme proclaimation against diagnosis, however, is contradicted later with: "I believe that the road to better outcomes will run through better diagnosis," a system that "needs to strive for precision, allowing each person to get the treatment most likely to work, not for a population but for that person." Yet the text recognizes that "in the push for progress, we are up against more than biology. Negative attitudes about diagnosis and treatment may prove a greater challenge."

Beyond diagnosis, a redemption-sounding statement is made: "Social determinants such as poverty and life stress are often more important for outcome and unquestionably more actionable." We have known for a long time that the goal of every treatment modality in a multidisciplinary team approach (which the book does not mention, acknowledging instead "a medical approach to define the problem") must focus on "social and relational approaches."

Thus, installed in a clearly social alternative route toward the diagnostic characterization of mental conditions, the book analyzes the ways such conditions are managed by the general population. The most eloquent example is stigmatization ("the biggest problem in mental health"), the colophon of the fear, avoidance, and hyper-emotionality (to be read as hostility) associated with a mental disorder in oneself or in the family. In turn, the route toward recovery is marked by 3 features (the "3 Ps") that constitute one of the most relevant parts of the volume: people, place, and purpose. "Recovery," Insel noted, "is not just relief of symptoms; it's finding connection, sanctuary, and meaning not defined or delimited by mental illness."

Recovery, indeed, is going beyond a life determined by negative features, be it symptoms, neuronal misconnections, or "bad genes." It is restoration of social links that cannot, and should not, be viewed as a "basic biological need" like the book pretends. To explain loneliness, support, solidarity, attachment, or love as purely biological, brain-related phenomena is an exercise in rigidity and partiality, far from the integral focus of humanity and humanism. A transcendental summarizing phrase reads: "I have come to think of mental illness as a medical problem that requires a social solution."

"Recovery also requires a safe place to live," and place means availability, acceptance, and compassion as well as resources and workable norms. Purpose (the third P) means helping those with mental illness and dealing with the social surroundings and sequelae: "We need to engage people not just on what's wrong, but on what's strong."

TABLE. The 4 Stages of Progression

1. The period of risk before the onset of any symptoms
2. The prodromic period
3. The acute first episode
4. The disability linked to a chronic and pervasive psychosis

The closing section centers on the way forward, Pragmatic approaches such as integrated or coordinated specialty care are examples. Here, the book makes another courageous admission: When NIMH first proposed coordinated specialty care in 2008, Insel thought "the idea was boring because these interventions had been around for 3 decades." His first response: "Where is the innovation? I was still in the mindset that the breakthroughs we needed were high tech, not high touch."

Improvements is a tough challenge, but not impossible. Multidisciplinary teamwork, and peer and family members' incorporation "on a foundation of trust" are valid measures. Based on numerous experiences abroad—particularly in low- and middle-income countries—"the practical meaning of democratizing care" evolves into the delivery of quality care. Innovative options like the quest for the "quantified self" by software engineers are also enthusiastically described. And a positive use of "doomscrolling, privacy hacking, and toxic positivity" on social media could also begin, based on credible information and "a chance to connect…to close the 60% gap between need and care."

Telepsychiatry and related technological innovations are also mentioned as "providing information, connection, and convenience" to both patients and care providers. Increasingly sophisticated modalities are described, and "unavoidable and yet unresolved ethical and trust issues" are recognized. A more specific discussion of some of them (depersonalization risks, insight deficits, mechanization, and a pervasive and paradoxical sense of loneliness) would have been desirable.

Prevention and mental health promotion become the culminating stations of this arduous journey. In the former, tertiary prevention predominates, which is important for those who are already ill, but clearly insufficient for those potentially affected by mental conditions. The book assumes a positive position: Anyone could become exposed to triggering factors of mental illnesses; therefore "some of the skills learned in psychotherapy, like mindfulness, reframing, and emotional regulation, not only treat [post-traumatic stress disorder] (PTSD) and depression but could potentially help anyone. Why not teach them to everyone?…Why not try for herd immunity against depression and suicide?"

Mental health promotion is not specifically addressed. It covers political, legislative, administrative, and sociocultural territories that are theoretically implied and only mentioned as components of its main objective. It is not just the quality of care that matters: "Outcomes are worse because of the world outside of health care. It's our housing crisis, our poverty crisis, our racial crisis, our increasing social disparities that weigh heaviest on those with the greatest needs."

Insel writes: "mental health has become a measure of the soul of our nation." The undisputable meaning of this phrase is a true reflection of current realities in America and the world. He cited Donald M. Berwick, MD, MPP's, concept of "moral determinants of health" to deepen the analysis of the origins of the crisis, which is more than a medical challenge: "It is a social justice issue" whose seriousness is compared with the "separate and unequal" Jim Crow phase of American history.

The salience of sociocultural forces in health, sickness, and medicine has been recognized throughout the history of our discipline. Interestingly, *Healing* uses the words "culture" and "cultural factors" just a few times. Perhaps Insel considers *social* and *cultural* as synonyms, but they are not: *Social* entails a broader territory, closer to notions and concepts of public health and collective impact, while *cultural* encompasses unique features engendered throughout the history, traditions, language, arts, and religions of human groups across the world.

In short, *Healing* contains several highly valuable lessons. It shows us the perceptual, cognitive, and emotional evolvements of a figure of American psychiatry who led the strongest biological period of research with passion and conviction, promoting and defending it with scientific work and doctrine-guided strategies. More recently, he has utilized such experience as both an echo chamber of self-questioning and a source of needed answers. This process may have been painful at times, but its results can be saluted with respect and renewed hope. He discovered truths that others had written about but felt compelled to share them through printed evidence. The book becomes, then, a powerful self-revealing essay, an eloquent documentation of personal reflections, a catalog of clinical and social realities, and an agenda for a collective journey that started many decades ago and that COVID-19—among other factors—has dramatically brought to the forefront.

Visit psychiatrictimes.com for more insights about this book and what it means for psychiatry.

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The Most Important Thing You Need to Know About Meta-Analyses

Randall F. Moore, MD, JD

A busy clinician does not have time to read the vast number of randomized controlled trials (RCTs) published about different treatments. But good meta-analyses save us time by aggregating and summarizing data from relevant trials. Individual RCTs are sometimes small and suffer from methodological flaws. The results of RCTs are often influenced by sampling error. Good meta-analyses help us base decisions on larger numbers of subjects and reduce the effects of sampling error. To make the most of meta-analyses, we need to understand the most important information reported by a good meta-analysis. That information is the "prediction interval." Although meta-analyses can focus on other topics, this article focuses on meta-analyses of treatments.

Using clear rules, a systematic review searches for studies on certain interventions for certain medical conditions. The authors of the study review the data from relevant studies to determine if helpful patterns can be found.

A meta-analysis is a systematic review that also includes a statistical synthesis of the data and calculation of overall, or "summary," effect sizes. Thus, meta-analyses allow us to base treatment decisions on the best possible evidence determined from a thorough search for the evidence.

The summary effect tells us if a treatment's average effect is clinically meaningful. But different patients and different populations of patients respond differently. Some patients will experience a below-average effect, some about an average effect, and some an above-average effect. Further, different studies report different average effect sizes. We need to know to what degree the effects are consistent or inconsistent. In meta-analysis, the degree of consistency or inconsistency is referred to as "dispersion" or "heterogeneity."

Dispersion

Dispersion exists for 2 reasons: dispersion of true effects sizes and dispersion secondary to sampling error. True dispersion exists because different RCTs differ in at least 3 ways. First, different RCTs may include different subsets of a population (eg, 1 study may provide a particular drug to patients aged 18 to 64 years, and anoth-

FIGURE 1. Normally Distributed Study-Level Means

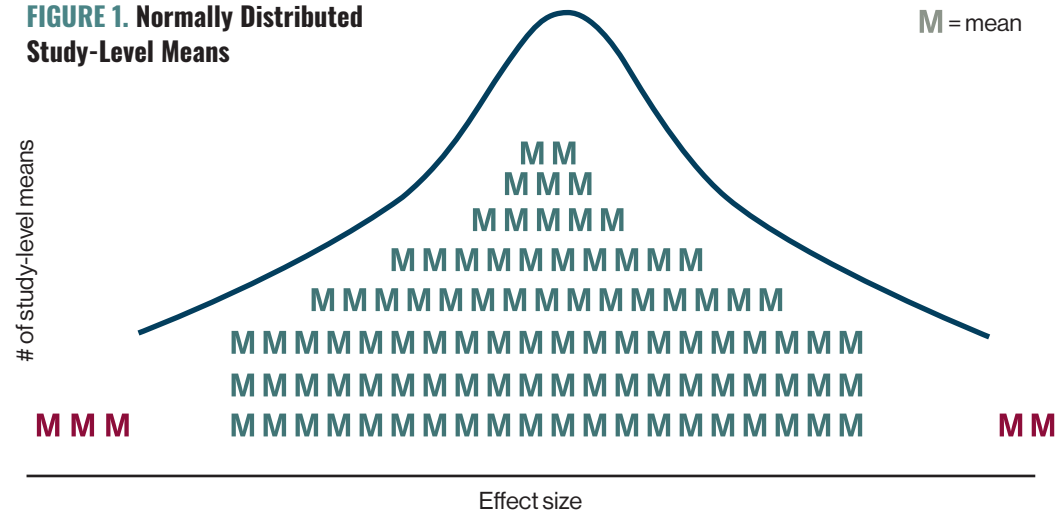


FIGURE 2. Using the Prediction Interval in Clinical Practice

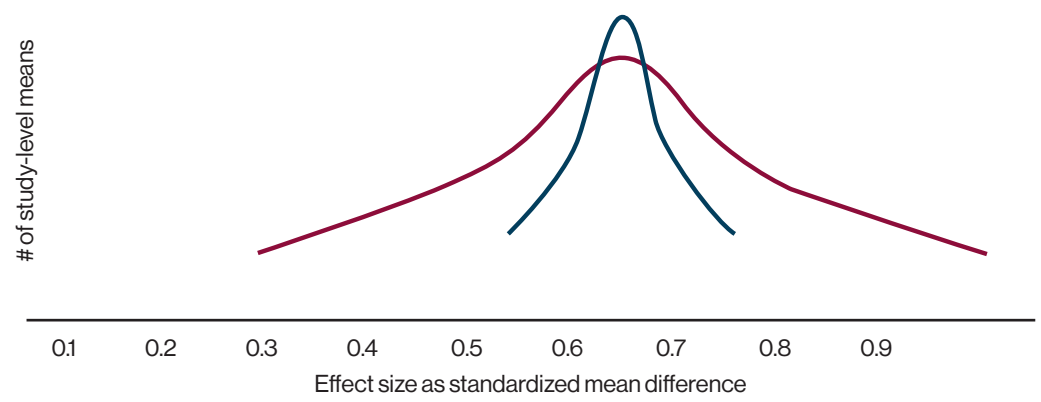
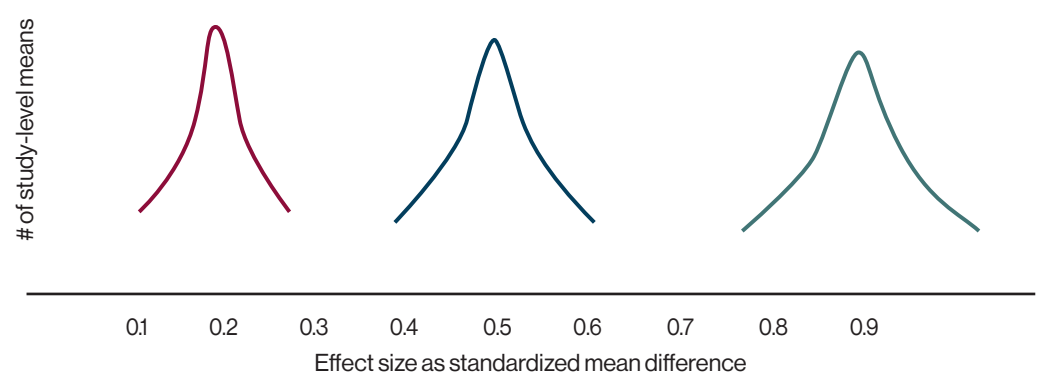


FIGURE 3. Using the Prediction Interval to Choose Among 3 Treatments



er RCT may provide the same drug to patients over aged 65 years). Second, RCTs are conducted according to different protocols (eg, 1 RCT may provide a form of psychotherapy for 12 sessions, and a different RCT may provide the same form of therapy for 20 sessions). Third, experimenters vary in their degree of skills in providing the treatment and in conducting the RCTs.

Dispersion due to sampling error occurs simply by chance. The sample drawn may not accurately reflect the population. For example, in a certain city, the population of individuals with depression may include 30% of patients who are 65 years and older. However, just by random chance, an experimental sample of patients with depression drawn from that city might consist of 45% of patients who are 65 years and older. If the RCT involves treating the patients with an antidepressant, the effect size may be reduced by the sampling error, given that older patients are less likely to respond to antidepressants.

We want to statistically eliminate the effect of sampling error and to know the dispersion of true effects. The prediction interval (PI) is the statistic that does this.

Prediction Interval

To fully explain the PI, we would have to see the equations and discuss them extensively. We do not have space for that, and the math is complex and requires many layers of computation. Instead, let's introduce the concept and look at it graphically.

The equation for the PI is based on the standard deviation of the mean effect sizes of the included studies. A PI is defined with a level of statistical significance, usually P = .05, in which case, we have a 95% PI. Assume we did 100 more studies. Every study would have its own mean effect size, m_1, m_2, m_3, etc, all the way up to m_{100}. Those 100 study-level mean effects sizes would vary from study to study. For a 95% PI, 95 of the studies would have a study-level mean effect size that fits somewhere between the low end and the high end of the PI. Five of the 100 studies would have a study-level mean effect size that is below or above the PI. If the study-level means were normally distributed, the distribution would look something like the graph in **Figure 1**. The blue curve represents the bell curve of a normal distribution of study-level means. The PI extends from the left end of the bell curve to the right end of the bell curve. There would be 95 green study-level means that fit within the PI and 5 red study-level means that fall outside the PI.

Let's continue to look at the PI graphically and see how we can use the PI in clinical practice. In **Figure 2**, let's assume that the curves reflect different treatments and that each curve reflects the synthesis of a statistically sufficient number of studies—say 10 or more. Assume that the curves reflect dispersion of true effects because we have eliminated the effects of sampling error. That is, the curves illustrate normally distributed PIs. The green curve and the red curve have the same mean effect size. Assume that the average effect sizes are clinically meaningful at 0.65 on the X axis, but that any effect below 0.5 is not clinically meaningful. The red curve is much broader. The effects are highly dispersed and inconsistent (heterogeneous), and a substantial portion of the red curve extends below the clinically meaningful effect size of 0.5. If we did many studies, a considerable portion of them would find a true mean effect size below 0.5. If we provide the red treatment, there is a substantial chance our patient will not achieve improvement of at least 0.5.

In contrast, the green curve is much narrower. The results of the included studies are much more consistent. Even the leftward aspect of the green curve is above the clinically meaningful effect size of 0.5. If we provide the green treatment, we can be more confident that our patient will improve.

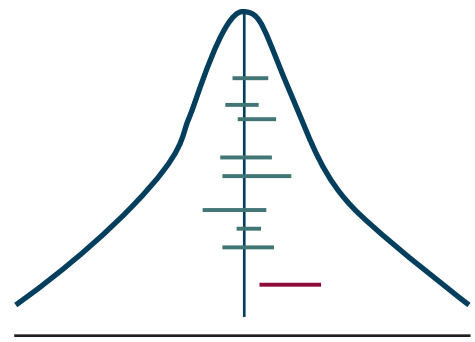
In **Figure 3**, let's look at some further examples to understand how we can use the PI. Again, assume that each curve represents the PI from a meta-analysis of 10 or more studies. Assume that the studies included substantial numbers of patients such as one for whom you need to develop a treatment plan. None of the red curve crosses over the clinically meaningful effect size of 0.5. This treatment is not likely to work. The blue curve straddles the clinically meaningful effect size. This treatment may or may not work. All of the green curve is above the clinically meaningful effect. This treatment is likely to work.

Of course, we cannot just look at numbers about treatment effects. In making clinical decisions, we also have to consider other factors, such as how serious the underlying medical condition is, the severity and probability of potential adverse effects, economic costs, all of those same factors about alternative treatments, and how likely it is that alternative treatments would work.

TABLE. The Differences Between PI and CI

CONFIDENCE INTERVAL	PREDICTION INTERVAL
Based on the standard error	Based on the standard deviation
95% CI = M_C ±1.96SE	95% PI = M_C ±1.96SD
Based on the combined mean of all the studies and reflects how confident we are in the estimation of the true mean of the entire population of patients who could theoretically be treated	Reflects the spread of the **study-level means**; this estimates the dispersion of true effect sizes
Limited utility in making clinical decisions	Very important in making clinical decisions

FIGURE 4. Distinguishing Prediction Interval and Confidence Interval



Prediction Interval vs Confidence Interval

Unfortunately, many—if not most—meta-analyses fail to report the PI. This omission makes it really hard to apply the results to clinical decision-making. Many, if not most, meta-analyses report the confidence interval (CI) and claim that this statistic represents dispersion or heterogeneity of true effect sizes. However, this is incorrect.

Whereas the PI is calculated from the standard deviation, the CI derives from a different statistic: the standard error of the mean. The 95% PI = M_C ±1.96SD, where M_C is the mean effect of all the studies combined and SD is the standard deviation. The 95% CI = M_C ±1.96SE where SE is the standard error. The CI reflects how confident we are in the estimation of the combined average effect size. We summarize the differences between the PI and the CI in the **Table**.

Let's look at this graphically as well. Imagine that our population of interest is everyone in a particular city with depression and that we treat every patient with depression in a placebo-controlled trial. Assume that the bell curve in **Figure 4** illustrates the dispersion of the true effect size based on treating everyone in the population. Now imagine more realistically that we complete a series of studies of samples of patients from this population. A 95% CI means that if we did 100 studies, in 95 of those studies the CI would include the true mean of the entire population, but 5 of the CIs would not include the true mean. In Figure 4, the vertical line represents the true mean effect of the total population of individuals with depression in our city of interest. The horizontal lines represent the CIs of the individual studies. The CIs vary in width. If we did 100 studies, for 95 of them the CI would cross over the vertical line. Five of the CIs would not cross over the vertical line. In Figure 4, the green lines represent the 95 CIs that include the true mean effect size of the population. The red line represents the 5 CIs that do not include the true mean effect size

of the population.

As the number of studies grows, the CI narrows and that means we are more confident in how well we have estimated the true mean effect of treating the entire population. But just being confident in the mean effect size does not tell us how dispersed or how consistent the effects are overall. To make clinical decisions, we want to know how broad the base of the bell curve is and where the bell curve fits compared with a clinically meaningful effect. The PI tells us this information.

Many, if not most, meta-analyses report the inconsistency statistic I^2 (also called the heterogeneity statistic) and claim that this statistic represents dispersion or heterogeneity of true effect sizes. However, this is incorrect. I^2 is not an absolute number. I^2 is the following ratio:

$$\frac{\text{total observed dispersion (including sampling error) – dispersion due to sampling error}}{\text{total observed dispersion}}$$

An analogy might help us understand why we want to focus on an absolute amount and not a ratio. Imagine that you ask me, "What are your total financial assets?" I answer, "My house constitutes 25% of my total assets." You asked about an absolute amount, but I answered in terms of a ratio. My house might be worth $100,000, and my total assets might be $400,000. Or my house might be worth $500,000, and my total assets might be $2,000,000. Either way, the ratio by itself does not answer your question about the absolute amount of my total assets.

I^2 is reported as a percentage. According to different cutoff points, I^2 is described as low (about 25%), medium (about 50%), or high (about 75%) heterogeneity. This practice is illegitimate and should be abandoned.

Concluding Thoughts

There is much more we could discuss about meta-analyses, but it is the PI that best informs clinical decision-making. Do not worry too much about the math. Use the PI intuitively. Determine what you believe is a clinically meaningful effect size, and then graph the PI. Then compare the curve of the PI to that of the meaningful effect size. Finally, estimate whether the treatment is likely to help your patient at issue.

For more information, see Borenstein et al, *Introduction to Meta-Analysis*, 2nd Edition.

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Exploring Meta-Analyses: An Example

Randall F. Moore, MD, JD

(This article addresses methodological and statistical concerns about a recent study titled "The Serotonin Theory of Depression: A Systematic Umbrella Review of the Evidence."[1] For further discussion, please see the analysis by Ron W. Pies, MD, and George Dawson, MD, in last month's issue of *Psychiatric Times*™.[2])

The brain is the most complicated thing in the universe. Problems with the brain, such as depression, are also complex and involve manifold factors including genes, other biological conditions, general medical conditions, past and current environmental exposures, and psychological capabilities and weaknesses. Multifactorial causation means it will always be hard to detect the signal of a single contributing cause. Lack of proof or imperfect proof of a derangement having a causal role is not proof of a lack of causation.

A good review is based on an exhaustive search for data. The review by Moncrieff et al looked at only 3 databases. When the authors found more than 5 reviews or large analyses, they included only the most recent 5. The investigators did not find a systematic review or meta-analysis on serotonin depletion within the last 10 years and so included only the 10 most recent studies.

Unfortunately, the review misrepresented some of the statistics.

FIRST, see the Moncrieff et al Table 2, in which "No effect" was listed based on 95% confidence intervals. As described in the companion piece in this issue, confidence intervals shrink as the number of included studies increases. More importantly, confidence intervals measure only how well we have estimated the mean. Confidence intervals do not measure heterogeneity, which is what we want to know in interpreting whether a result might represent a meaningful effect in some populations.

SECOND, the review in question did not report the prediction interval, which is the statistic that represents heterogeneity. It may be that the underlying meta-analyses and studies sometimes did not report prediction intervals, but if so, that should have been noted to address heterogeneity.

THIRD, in the Moncrieff et al Table 1, the I^2 statistic is listed as a measure of heterogeneity, but I^2 is a ratio, not a measure of absolute heterogeneity.

FOURTH, effect sizes are more important than statistical significance. The review dismissed findings as statistically insignificant by calculating p values relative to confidence intervals. However, as previously noted, the confidence interval is not even the correct statistic to test. In the Moncrieff et al Table 1, some of the effect sizes, such as those found by Wang, Nikolaus, Kambeitz, Gryglewski, and Ruhé, are of modest to large size considering that we expect any 1 factor to be only 1 of many contributing to a condition such as depression.[3-7]

Unfortunately, the investigators performed only a review and did not complete a statistical synthesis of the data. Thus, the most we can draw from the review are nonquantitative impressions. Unfortunately, the impressions are not trustworthy given the misinterpretations of the statistics.

The review did not say anything about the possibility that derangements in serotonin functioning could be 1 factor among many that contribute to a loss of neuroplasticity, which may be an important unifying principle in understanding depression.

We should trust studies and reviews only when their methodology and statistics are sound. When the methodology and statistics are not sound, as in this case, the study and its conclusions must be treated with skepticism at minimum and potentially even disregarded completely.

Dr Moore is clinical associate professor of psychiatry at Texas A&M University College of Medicine and works at the Baylor Scott & White Health Mental Health Clinic in Temple, Texas.

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Psychiatric Times | Around the PRACTICE

Management of Adults with ADHD

"Around the Practice: Management of Adults With Attention-Deficit/Hyperactivity Disorder (ADHD)" is out now.

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Around the PRACTICE

Tackling Treatment Issues in Adult ADHD

Heidi Anne Duerr, MPH

From fallacies to frustrations, experts shared insights on adult attention-deficit/hyperactivity disorder (ADHD) in a recent custom *Around the Practice* video discussion.

"There is controversy about how often ADHD persists from childhood into adulthood," said panelist Andrew J. Cutler, MD. "In my clinical experience, the presentation can wax and wane, either the symptomatology or the impairments. Sometimes it has to do with the environment, its stressors, and various things going on." Cutler is clinical associate professor of psychiatry at SUNY Upstate Medical University in Syracuse, New York, and the chief medical officer of the Neuroscience Education Institute.

Cross-sectional studies also suggest a waxing and waning of symptoms in adults with ADHD, according to moderator Stephen Faraone, PhD, who is distinguished professor of psychiatry at SUNY Upstate Medical University in Syracuse, NY. Faraone noted about one-third of adults with ADHD will not appear to have ADHD if examined at a single point in time, because symptoms and functional impairments may change depending upon what is happening in patients' lives.

"I kind of think of multiple sclerosis, this remitting-relapsing picture. That's how I explain it to my patients," added panelist Theresa Cerulli, MD, president and medical director of Cerulli and Associates. "It is rarer to see somebody go into 'remission' and stay in remission... It really is this kind of a sine wave with the longitudinal perspective."

Thus, the panel agreed it is important to ensure patients are doing well and, if not, that they are given the treatment support they need. "If a patient has had history of ADHD and, after a period of time, they are only showing a few symptoms and they're still impaired, they still have ADHD. We don't require that they have the full symptom count to allow treatment," Faraone said. "It would be a mistake to deny [them] treatment."

Similarly, there is a misconception that adults who are successful and high-achieving cannot have ADHD. "I have had more than a few colleagues tell me that a patient thinks he has ADHD, but [the patient] went to medical school or went to law school and he is a high achiever, so how can he possibly have ADHD?" Faraone said. "There is actually a lot of research which... shows that people who have high IQs and ADHD are doing worse in life than people with high IQs who do not have ADHD. They do need help and should get it. We shouldn't discriminate against high IQ people because they are good achievers, because they can do better if they are properly treated."

Comorbidities Complications

"About 75% of the time, if you're diagnosed with ADHD, you are going to have at least 1 comorbidity; and the data shows 60% of the time you are going to have 2 or more comorbidities," Cerulli noted. "The complex medical histories that many of our adults can present with can become very challenging—people that have problems with blood pressure other cardiovascular diseases in adulthood—and we want to be very careful."

Depression and anxiety are often comorbid psychiatric conditions, she added. And patients with both psychiatric and medical conditions "is more the rule of thumb than not."

Faraone added that ADHD shares genetic risks and therefore comorbidity with somatic disorders, especially cardiometabolic conditions such diabetes and obesity. What makes matters worse is that the diabetes appears not to be as well managed when ADHD is not being managed.

Sleep issues are also common, although it often is not considered apart from the medications' effects. "I think many practitioners don't realize that, although insomnia and sleep problems are side effects of some ADHD medications, they're also associated with ADHD in the absence of medication," Faraone explained. "That's been shown now by many studies and meta-analyses; it's as strong as data gets. Patients need to be evaluated for preexisting sleep disorders. In some cases, if patients have sleep apnea and are treated, ADHD symptoms will be reduced pretty dramatically, with an effect size similar to a nonstimulant."

Choosing Treatments

Cutler noted that treatment choices are somewhat limited, adding that the available stimulant molecules (amphetamines and methylphenidates), both have similar and, importantly, very high effect sizes. There are some differences in how they work, he said, although they both block the reuptake of norepinephrine and dopamine.

"It is interesting that there are some patients who do better with one than the other; either they have a better response, or they tolerate one better than the other," Cutler said. "One of the points I always like to make to clinicians is if you've been using methylphenidate, and the patient is not doing well, please switch over to the other—to the amphetamine. Always make sure you have tried both before you give up on them."

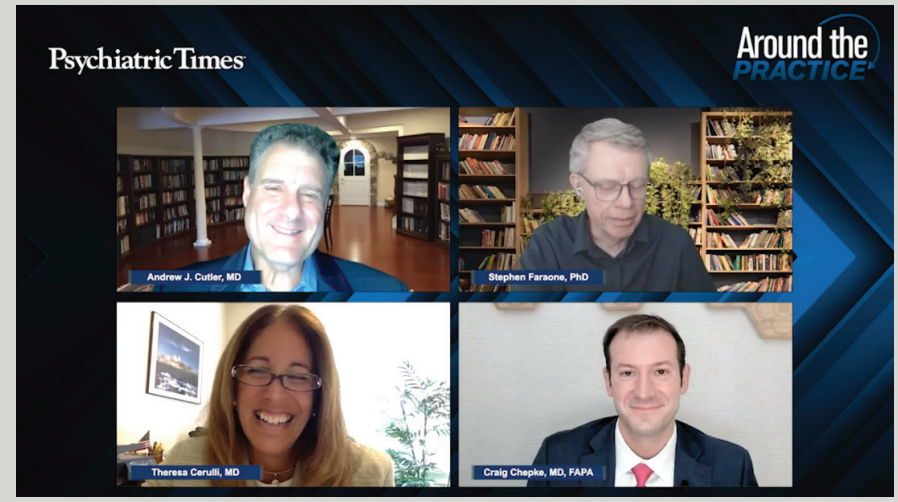
There are safety and tolerability issues associated with stimulants, including insomnia, irritability, decreased appetite, cardiovascular risks, and the possibility of worsening psychiatric conditions, such as psychosis and mania. Plus, the panelists noted that stimulants carry a risk of abuse and diversion, although it is less likely with the long-acting varieties.

"I'm very, very much in favor of using extended-release formulations," Craig Chepke, MD, FAPA, shared, adding that they are not all created equal and have changed over the years.

"An extended release from just 10, 15, 20 years ago is very primitive, compared to what's coming out today," said Chepke, Medical Director at Excel Psychiatric Associates, PA, and clinical assistant professor of psychiatry at State University of New York Upstate Medical University. "You've got a V-6 engine in 1969, versus a V-6 in 2022. You're going to have a lot better parameters for this newer engine than you did for the old one."

"I completely agree, Cutler said. "The newer [stimulants] tend to have a lot of superior delivery mechanisms. And that translates into a superior pharmacokinetic profile."

"If someone did have a problem—where one extended release formulation was too long-acting for them—we can switch them to a shorter-acting, extended release formulation," Chepke explained. "And vice versa: If it's too short of a short-acting, we don't need to necessarily add a booster of an instant release, as has been com-



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mon in the past. We can switch to a long-acting stimulant that is extra-long acting."

Chepke noted patient education is important, especially when prescribing the long-acting varieties. "Some patients will want to go back to an instant release because they can tell when it is working," he said. "And what I have to tell them is that's not a good thing; that's a buzz, that's not a therapeutic effect you're feeling. And you don't need that buzz to have efficacy."

There are also nonstimulants, including alpha-2 agonists and norepinephrine reuptake inhibitors, the panelists noted. Both are not controlled substances and both are considered effective—just not as "universally effective" as the stimulants. Cutler explained, "They don't work for everybody, obviously, but they have a lot less of some of the baggage of the stimulants."

There are some factors that should be considered when prescribing these agents, Cutler added. "If we're talking about the norepinephrine reuptake inhibitors, we do have issues with blood pressure. They also have bolded warnings about suicidality. There are warnings around somnolence sedation as well, and you do have to worry about activation and the possibility of mania."

Interestingly, the alpha-2 agonists have an opposite profile, he said, adding those medications are alsoused for hypertension. "We worry about lowering blood pressure, not increasing blood pressure," Cutler commented. "And when used by themselves, they can be quite sedating." Culter added these agents are currently only approved for children, not adults.

What about deciding between stimulants and nonstimulants? "We have to think about the risk/benefit ratio when we're prescribing," Chepke explained. "When I'm confident that someone has ADHD, it justifies the risk, in my mind, to prescribe stimulants because it is risky for non-treatment. However, when I'm not confident in that diagnosis of ADHD, that changes my risk/benefit calculus, and so nonstimulants rise in my decision tree."

Cerulli also likes to consider comorbid conditions. If depression also presents, she might consider a nonstimulant that has some benefits for mood. "I like to collaborate with the patient, and say, 'I'm going to be transparent in what I'm thinking, and there isn't a right or wrong. You could say to me, 'Look, no, I know I'm depressed, but I know the reason I'm depressed is that my ADHD is out of control. and I know in my life when I have my ADHD better managed that the depression goes away.' Then I would change the order," she said.

Simularly, Cerulli is cautious about prescribing stimulants for patients with comorbid anxiety. "I'm not a big fan of combining anti-anxiety medications and stimulants as usually the risk with stimulants of worsening some anxiety symptoms in somebody already prone to anxiety. Depending on the patient and the situation, I'm just more careful before I go that route."

Cutler reminded his colleagues that sometimes that anxiety is due to untreated or undertreated ADHD. "Sometimes you have to tease out the chicken and the egg. I have many patients—as I'm sure you do, too—who when I treat the ADHD, the anxiety gets better because a lot of the anxiety is that overwhelmed feeling," he said. "They can't keep track of things. They are always worrying: 'What did I forget? What am I going to lose? What kind of mess did I make out of things?' So, I think you have to carefully tease things out."

Unmet Needs and Wish Lists

"Although we have dozens, literally, of stimulants, and we have some nonstimulants as well, we still don't have enough treatment options," Chepke said. "One aspect is the small range of molecules that we have... And each one of those has certain pharmacokinetic limitations."

Cutler agreed, saying additional options could potentially address safety profiles, too. "As people get older, I'm very concerned about cardiovascular issues, and other medical conditions, drug-drug interactions—because they're on multiple medications. And the 2 approved nonstimulants—the norepinephrine reuptake inhibitors—have warnings about blood pressure and heart rate, as do stimulants."

Additionally, Cutler would like to see options that address diverse symptomology, like executive function. "This is a big part of ADHD, especially in adults. And so medications that work for that [would be useful]. "

Cerulli added "robustness" to her wish list. "What I would like to see is a nonstimulant—or *noncontrolled* is probably better word—a noncontrolled medication for ADHD that is available 24/7," she said. "It's going to be there from the time you wake up in the morning until the time you put your head on the pillow in the evening."

"I think also one that works consistently," Cutler added. "My sense is that stimulants work pretty reliably for the vast majority of patients, and I think studies suggest it's up to 80%, but nonstimulants are maybe more 40% to 60% of patients. So something that's a little more consistent in more patients, too."

Precision medicine—the ability to predict who responds to what medication—is on Faraone's wish list. "We need to be able to have something that tells the clinician there's a good chance that this person is going to do well on this nonstimulant or this is formulation. We are not there yet, but I do expect we are going to get there in 5 or 10 years."

"What we need, of course, are probably some newer mechanisms that go beyond the traditional monoamines of norepinephrine and dopamine," added Cutler, who is currently working on a triple reuptake inhibitor."

Concluding Thoughts

Because there are no treatment guidelines for ADHD in adults in the United States, clinicians should keep the patient in the center of their treatment decisions, the panel agreed. That means individualizing treatment for efficacy and adherence as well as lots of patient education.

"It helps if you've got buy-in from the patient in the beginning," Cerulli said. "You make that decision together, and you know there's sort of a flow chart in both of your minds. If this isn't a good fit, we know what to do next, and we know why we're picking this one. If it is a 'we' decision, the chances of adherence are going to go up."

She relies heavily on psychoeducation, not just to help them with their symptoms, but also in general to help patients with their lives, their relationships, and their education/school and work. That is how you can take the whole picture into consideration, she explained.

"It's not just about symptom control. That is one small piece," Cerulli concluded. "The overall goal is having the patients' lives improve, be better."

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LEARNING OBJECTIVES

After engaging with the content of this CME activity, you should be better prepared to:

Gain a better understanding of complex factors that result in mental health problems in the context of the COVID-19 pandemic.

Gain knowledge of evidence supporting complementary and alternative medicine (CAM) interventions for enhancing resilience during periods of prolonged isolation and for treating mental health problems associated with the COVID-19 pandemic.

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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COVID-19 & Mental Health: Global Consequences and CAM Approaches

James Lake, MD

As the virus that causes COVID-19 illness (SARS-CoV-2) continues to mutate, we continue to see high rates of COVID-19 illness with concomitant neuropsychiatric symptoms including depressed mood, anxiety, posttraumatic stress disorder (PTSD), and other mental health problems. Medical and psychiatric comorbidity are expected to have serious long-term consequences for global public health and mental health.

Although there is no evidence that natural supplements or other complementary and alternative medicine (CAM) interventions prevent or treat medical illnesses caused by SARS-CoV-2, preliminary findings suggest that select supplements and other CAM approaches (**Figure**[1]) may have beneficial effects on mental health problems associated with the pandemic.

Global Mental Health Impact of the Pandemic

Millions of individuals experience depression, anxiety, and worsening or new substance use disorders (SUDs) associated with the prolonged social isolation associated of the pandemic.[2] A systematic review of studies published between January 1, 2020, and January 29, 2021, estimated that an additional 53 million cases of major depressive disorder (MDD) (an increase of 27%) and an additional 76 million cases of anxiety disorders (an increase of 25%) globally.[2]

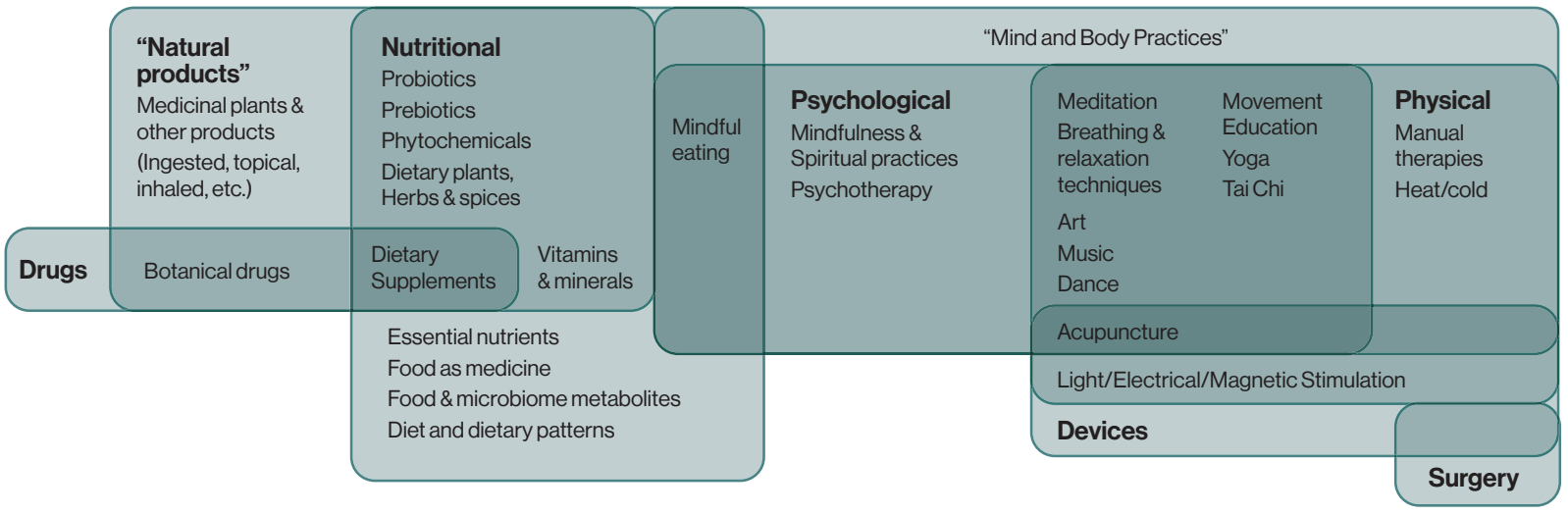
The mental health impact of the pandemic has been greater among women and younger individuals than among men and older individuals. Globally, additional cases of MDD and anxiety disorders attributed to the pandemic accounted for approximately 50 million disability-adjusted life years (DALYs) caused by MDD and approximately 45 million DALYs caused by anxiety disorders, representing billions in lost personal income and declines in the gross domestic product of many nations.

The impact of the pandemic on the mental health of children and adolescents has been especially severe. For example, in a systematic review of studies published in English between January 1, 2020, and February 22, 2021, (N = 116 articles; total N=127,923 children and adolescents), the authors found high rates of COVID-related fear, depressed mood, and anxiety compared with prepandemic estimates.[3] The review also found that older adolescents and girls living with chronic physical conditions were at greatest risk of experiencing negative mental health outcomes. Exercise, access to entertainment, positive family relationships, and social support were associated with better mental health outcomes.

Individuals with preexisting mental health problems have reported worsening of symptoms in the context of prolonged social isolation during the pandemic. For instance, a survey of adults (N=272) conducted in the first months of the pandemic found that individuals with preexisting anxiety or depressed mood experienced symptomatic worsening somewhat higher than in the general population.[4] Respondents attributed anxiety and depressed mood to prolonged social isolation from friends, family, and places of worship, and to being overwhelmed by unrelenting negative media coverage. In addition to the isolation, strategies used to reduce the spread of SARS-CoV-2 infection (ie, physical distancing and restricted travel) made it more difficult for patients to obtain treatment during the height of the pandemic.

The result was that many individuals with COVID-related mental health complaints did not seek conventional care during the height of the pandemic. Although these issues were exacerbated during the height of the COVID-19 pandemic, it has not yet been determined whether individuals with mental health problems were less likely to seek care during the pandemic in general.[5]

FIGURE. Examples of Psychological, Physical, and Nutritional Complementary Health Approaches[1]



Neuropsychiatric Complications of COVID-19

Research findings are revealing complex causal relationships between mental illness and COVID-19, with mental health issues grouped into 4 categories (**Table 1**).[6] Depressed mood, anxiety disorders, and other psychiatric disorders are both risk factors for and consequences of COVID-19 infection. For example, a large cohort study of more than 60,000 cases of COVID-19 found that individuals diagnosed with any psychiatric disorder had a 65% greater risk of contracting COVID-19 compared with a matched cohort with no preexisting psychiatric disorders.[7]

Neuropsychiatric complications of SARS-CoV-2 infection are believed to be mediated by a variety of biological and environmental factors including systemic inflammation, direct viral damage to the brain, severe cytokine storm causing disruption of the integrity of the blood-brain-barrier, micro-infarcts, and thrombi in the brain, liver inflammation, impaired renal function, impaired oxygenation of the brain, viral-induced immune reactions and auto-immunity, and prolonged social isolation.[8] In cases of acute illness, these factors can manifest as a multifactorial delirium.[8] Delirium has been reported in approximately 30% of individuals hospitalized for management of severe COVID-19 illness.[9]

Older individuals are at greater risk of COVID-19-related delirium as well as acute and long-term neuropsychiatric disorders following COVID-19 illness.[8] Even mild or asymptomatic infection may result in delirium, cognitive impairment, extreme fatigue, and depressed mood. A study that followed US adults for 3 months after having acute COVID-19 illness found that 18% were diagnosed with a psychiatric disorder, with one-third being newly diagnosed.[10,11]

Young adults, Hispanics, African Americans, and individuals with preexisting psychiatric disorders are at higher risk of worsening mental health in the aftermath of acute COVID-19 illness.[12] One study found that roughly one-third of patients hospitalized for severe COVID-19 illness experienced memory loss and impaired concentration 3 months following discharge.[13]

One-fourth of adults admitted to ICUs with respiratory failure or shock experienced global cognitive difficulties equivalent in severity to mild Alzheimer disease 1 year following discharge.[14] Similarly, there is a common complaint of persisting "brain fog" following milder COVID-19 illness.[10,11]

One month following acute COVID-19 illness, roughly one-third of patients report having a depressed mood, 20% to 42% report having anxiety, and as many as 20% report having obsessions or compulsions.[15] Depressed mood and anxiety are reported more often by women, and those with severe COVID-19 illness, physical discomfort following acute illness, elevated inflammatory markers, and/or a history of psychiatric illness.[15,16]

PTSD is also common. Roughly 20% to 30% of individuals who have been hospitalized for management of severe COVID-19 symptoms have PTSD.[17-20] The highest risk of PTSD is associated with younger age, female gender, ICU care, and prior history of mental illness.[20] COVID-19 and PTSD share many of the same risk factors including high rates of medical comorbidities such as obesity, diabetes, metabolic syndrome, chronic pulmonary disease, cardiovascular disease, and autoimmune disease.[21-23]

Psychosis related to the COVID-19 pandemic has been attributed to multiple factors. A small percentage of individuals hospitalized for management of severe COVID-19 symptoms develop new-onset psychosis. There are reports of high-dose corticosteroids (used to treat severe COVID-19 illness) precipitating psychosis.[24,25]

The COVID-19 pandemic has resulted in a significant increase in SUDs.[12] Individuals with SUDs are at higher risk of contracting COVID-19, are more likely to require hospitalization after becoming infected, and are more likely to have risk factors for severe COVID-19 illness (eg, obesity, type 2 diabetes, cancer, cardiovascular disease, and chronic liver and kidney disease).[26]

High prevalence rates of many psychiatric disorders call for studies on both conventional and CAM approaches aimed at reducing risk of COVID-19 infection; managing mental health problems associated with prolonged isolation; treating mental health problems that occur in the acute phase of infection; and managing mental health problems during the weeks and months following acute illness, or so-called "long COVID" (**Table 2**[27]).

In response to the complex medical, neurologic, and psychiatric sequelae of COVID-19

TABLE 1. The 4 Categories of Mental Health Problems Related to COVID-19[6]

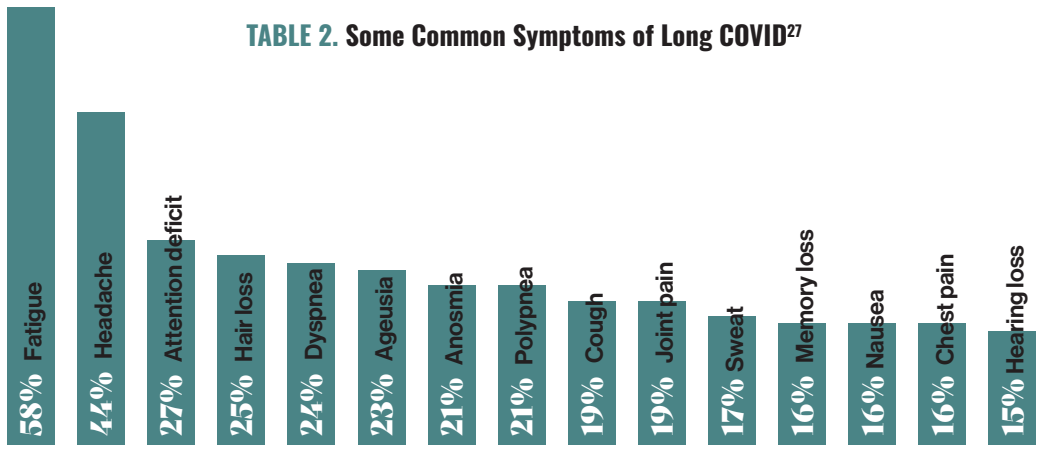
1. Problems that arise in the context of prolonged social isolation that are not caused by the virus (eg, depressed mood, anxiety, insomnia, and substance abuse)

2. Problems that take place during the acute phase of COVID-19 illness that are caused by deleterious effects of SARS-Co-V2 on brain function or through other affected organs, manifesting as symptoms of depressed mood, anxiety, PTSD, psychosis, and other psychiatric disorders

3. Persisting mental health problems following acute illness (ie, "long COVID") including worsening or new-onset depressive illness, PTSD, anxiety disorders, psychosis, and possible effects on cognitive functioning

4. Psychiatric symptoms or disorders such as depression, anxiety, insomnia, that result from an uninfected individual dealing with the illness, loss of function, or death of a family member or friend

TABLE 2. Some Common Symptoms of Long COVID[27]



illness, interdisciplinary clinics are being established in the United States to provide medical and mental health care to individuals with post-COVID syndrome.[9,28]

Although the subject of this review is CAM interventions, mainstream treatments including psychotropic medications and psychotherapies are also being investigated as potential treatments of mental health problems in all 4 categories of mental health issues associated with COVID-19 (Table 1).[6]

The Importance of Enhancing Emotional Resilience

In the context of limited access to care, studies show that many individuals struggling with mental health problems related to prolonged isolation benefit from mind-body practices, exercise, and proper nutrition. These self-directed approaches have been shown to improve resilience during prolonged periods of isolation and to lessen the severity of anxiety and depression associated with the pandemic. Positive lifestyle choices may also improve overall health, reducing the risk of contracting COVID-19, or lessening severity of symptoms in individuals who contract the virus.

A systematic review and meta-analysis of randomized controlled trials evaluated interventions aimed at improving mental health outcomes during and following illness caused by coronaviruses SARS-CoV-1 (SARS severe acute respiratory syndrome), Middle Eastern respiratory syndrome (MERS), and SARS-CoV-2/COVID-19.[29] The authors identified studies on a range of conventional and CAM mental health interventions, most of which were done in China or the United States. Most interventions were supported by low-quality evidence (ie, expert opinions and cross-sectional studies). Most of the interventions were aimed at preventing development of PTSD. Experts recommended individual psychotherapy, hotlines, and peer support groups for individuals diagnosed with PTSD, a frequent concomitant of acute illness with H1N1 and COVID-19.

Because benzodiazepines are known to worsen symptoms of PTSD, experts advised against the use of benzodiazepines to manage acute stress related to COVID-19 illness.[29] Among nonpharmacologic interventions, yoga, meditation, and breathing techniques were most often recommended. However, experts cautioned that mindfulness can sometimes worsen anxiety, depressed mood, and suicidality in individuals with moderate to severe symptoms.

Throughout the studies, the importance of positive lifestyle choices for maintaining good mental health in the wake of the pandemic were emphasized, including exercise, healthy eating habits, sleep hygiene, moderating alcohol consumption, and spending time with family and friends. Some experts recommended muscle relaxation and yoga to reduce anxiety and manage insomnia related to the pandemic. Despite a large body of evidence supporting the beneficial effects of spirituality and religiousness on mental health, only a few experts recommended spiritual or religious practices as coping strategies during the COVID-19 pandemic.[29]

Conventional Treatments of Mental Health Problems Related to COVID-19

Mainstream conventional treatments such as psychotropic medications and psychotherapy are helpful for treating mental health problems in the acute phase of COVID-19 illness and in the weeks and months following COVID-19, including during long COVID. However, to date there are no guidelines for conventional management of anxiety and depressed mood following infection with SARS-CoV-2.[30]

Mainstream treatments of psychiatric illness in medically ill patients may be appropriate for individuals afflicted with COVID-19. When managing psychiatric symptoms in hospitalized individuals who are acutely ill with COVID-19, use of established hospital psychiatry protocols is appropriate, including selecting psychotropics and dosages that pose the lowest risk of harm after accounting for organs that have been harmed by the virus.

For example, gabapentin is an appropriate and safe treatment for anxiety only in cases where renal function is not severely impaired.[8] In patients with decreased renal clearance, the dose of gabapentin should be adjusted accordingly.[31] Selective serotonin reuptake inhibitors (SSRIs) are a reasonable choice for patients who complain of both depressed mood and anxiety. However, fluoxetine, paroxetine, and fluvoxamine should be avoided due to the increased risk of drug-drug interactions; and paroxetine, fluvoxamine, venlafaxine, and desvenlafaxine should be avoided due to their short half-lives and unpleasant withdrawal symptoms.[8] Preliminary findings suggest that SSRIs, especially sertraline, may play an important role in managing COVID-19 infection through different mechanisms, including by ameliorating the cytokine storm syndrome, resulting in reduced levels of pro-inflammatory cytokines, increasing the number and functioning of immune cells, and possibly also through direct antiviral effects.[32] Pending confirmation by future studies, sertraline and other psychotropics may emerge as important treatments of COVID-19 illness.

CAM Approaches to Prevent or Treat COVID-19 Illness

Until late 2021, the absence of effective vaccines and pharmaceuticals for preventing and treating COVID-19 led to the widespread use of CAM interventions including botanicals, mindfulness, and energetic approaches.[33] To date there is no evidence that supplements prevent COVID-19 illness or have antiviral effects; however, clinical trials are ongoing to investigate putative antiviral or immune enhancing properties of select natural supplements including vitamin C, vitamin D, zinc, probiotics, and NAC (N-acetylcysteine).[34] Nonetheless, in less developed world regions where access to vaccines and pharmaceuticals remains limited because of availability or cost issues, millions of individuals continue to rely on CAM. Indeed, CAM approaches being used to treat COVID-19 are widely touted on social media and blogs; however, such "cures" are based on anecdotal reports often contextualized in highly politicized views of the pandemic. In fact, very few CAM interventions have been investigated in placebo- and sham-controlled studies, and there is no evidence to date that nutraceuticals or other CAM interventions kill the SARS-Co-V-2 virus, prevent COVID-19 illness, or mitigate symptoms associated with infection.

In an effort to correct erroneous claims about natural supplement "cures" for COVID-19, the National Center for Complementary and Integrative Medicine (NICCM) of the National Institutes of Health has published a fact sheet on dietary supplements being hyped as preventatives or treatments of COVID-19 illness. The NCCIM site, which includes links to detailed fact sheets for consumers and health professionals, states unequivocally that "there is no scientific evidence that any of these alternative remedies can prevent

One month following acute COVID-19 illness, roughly one-third of patients report having a depressed mood, 20% to 42% report having anxiety, and as many as 20% report having obsessions or compulsions.[15]

or cure COVID-19."[35]

The urgent global need to identify safe, effective, and affordable preventatives and treatments for COVID-19 illness has led to studies on a range of CAM approaches. An analysis of systematic reviews[36] of CAM interventions in COVID-19 illness identified 24 systematic reviews (21 for traditional Chinese medicine [TCM] herbals, 2 for vitamin D, and 1 for in-home activities). It found limited evidence that some TCM herbals may slow the rate of illness progression, no evidence that vitamin D improves major health outcomes, and modest evidence that exercise, yoga, and muscle relaxation techniques may improve mental wellness. The authors cautioned that findings are limited by inclusion of only those CAM interventions for which there were enough quality studies to permit systematic reviews; and the absence of a standardized methodology for evidence mapping.

A systematic review of studies on CAM interventions in patients with COVID-19 illness identified 14 studies (total N=972) and found evidence that acupuncture reduced chest pain; qigong increased physical activity and quality of life; and regular relaxation improved depressed mood, stress, anxiety, and sleep quality.[37] A review of studies on self-directed CAM interventions used during the pandemic found evidence that spending time in nature ("forest bathing") and maintaining a healthy diet, mindfulness, and regular sleep improved the immune response to the SARS-CoV-2 virus and general emotional well-being.[38]

Treating Mental Health Problems Associated With the Pandemic

Because of limited or no access to vaccines and antivirals in many countries, and shortages in personnel and clinics equipped to triage individuals in the acute phase of illness and individuals with long COVID, CAM interventions—when found effective—can play an important role in preventing and recovering from COVID-19 illness by enhancing resilience, reducing depressed mood and anxiety, and improving sleep quality. Identifying promising CAM interventions is an important global public health strategy because it is likely that future pandemics also will result in widespread mental health problems in the face of limited mental health resources. Finally, it is germane to note that the desperate global search for cures has led to a veritable epidemic of unsubstantiated CAM practices that may place large populations at increased risk of illness or death. This has been especially problematic in less developed world regions such as Africa.[39]

Although there is presently no evidence that natural supplements prevent or treat COVID-19-related medical illness, select natural supplements are being investigated as potential treatments of mental health problems associated with the pandemic. Other CAM modalities such as mindfulness, exercise, yoga, and biofeedback are being investigated for their potential role in enhancing emotional resilience or mitigating symptom severity of depressed mood, anxiety, and other mental health problems (**Table 3**).

TABLE 3. Types of CAM Treatments Marketed for COVID-19 Mental Health Issues

- Nutrition
- Natural supplements
- Exercise
- Traditional Chinese medicine
- Mindfulness and mind-body practices
- Biofeedback

Nutrition

Optimal nutrition boosts immune function and plays an important role in preventing and treating moderate to severe respiratory and non-respiratory infections, and should be embraced as a preventive strategy for reducing risk of severe COVID-19 illness, particularly among older individuals in nursing homes and those with chronic medical conditions.[40] For example, there is evidence that vitamins A, B complex, C, D, and E and select trace elements such as iron, zinc, selenium, magnesium, and copper have immune-boosting properties, and that dietary deficiencies of these micronutrients could interfere with immune function in response to viral infections.[41]

Older individuals in nursing homes are at increased risk of contracting COVID-19 and should be provided with specialized nutritional support including regular nutritional screening; dietary counseling; supplementation with essential vitamins and minerals including RDAs of vitamins A, D, E, C, B_6, and B_{12}; iron; zinc; selenium; and omega-3 PUFAs. Medically indicated malnourished older adults should be provided enteral and parenteral nutritional support.[42] Poor nutrition in low-income communities and less developed countries is associated with increases in morbidity and mortality in general, and this situation has become worse in the context of the severe economic impact of the COVID-19 pandemic.[43] The World Health Organization (WHO) should work with the governments of low-income countries to develop strategies to ensure access to optimal nutrition to boost immune function, especially for individuals who are severely ill.[44]

Exercise

A multinational cross-sectional analysis done in the United Kingdom, Ireland, New Zealand, and Australia during the initial stages of lockdown found that adults who reported exercising less before or during the COVID-19 restrictions reported poorer mental health and well-being.[45] This finding was consistent across all countries. Females reported more positive changes in exercise and corresponding improvements in mental health compared to males, and young adults reported more negative changes and poorer overall mental health compared to other age groups. Individuals who reported no change or a positive change in exercise starting before or during pandemic restrictions reported better mental health compared to those who reported negative changes in their exercise routine.

These findings are consistent with those of a US study in which adults who did not meet recommended guidelines for regular physical activity and engaged in greater screen time reported more depressive mood symptoms and stress.[46]

Mindfulness and Mind-Body Practices

Studies in China on individuals hospitalized for COVID-19 reported that mindfulness, relaxation, and progressive muscle relaxation reduced the severity of anxiety and depressive symptoms.[47-49] An observational study conducted online in China during the early stages of the pandemic found that regular mindfulness meditation was associated with improvements in pandemic-associated depressed mood, anxiety, and stress.[50] In a 10-day study conducted during the pandemic (N=64), healthy adults randomly assigned to brief daily mindfulness training experienced greater well-being and were less negatively affected by exposure to COVID-19 news compared with individuals assigned to a wait list.[51] The 2 groups did not differ in other measures including negative affect, anxiety, and depressed mood.

Tai chi has beneficial effects on physical and mental health, including increased aerobic capacity, improved balance, and improved sleep. There is evidence that the regular practice of tai chi may enhance immune function and improve pulmonary function in individuals with chronic obstructive pulmonary disease (COPD). The results of small nonclinical studies suggest that tai chi may reduce symptoms of anxiety and depressed mood.[52] Studies have also demonstrated preventive effects of regular tai chi practice on depressed

mood and anxiety.[53,54]

Natural Supplements

A narrative review of more than 50 herbals used in traditional systems of medicine to prevent or treat medical or neuropsychiatric complications of COVID-19 illness found limited evidence from in-vitro studies and anecdotal reports for select herbals or herbal formulas.[55] The authors emphasized that preclinical studies are needed to investigate mechanisms of action and confirm safety before it is appropriate to use any herbal medicines to prevent or treat COVID-related illness. They cautioned that safe medicinal uses of herbals are limited by frequent adulteration, contamination, toxicity risks, potential drug-herb interactions, and lack of standardization of many herbals.

At the time of writing, no placebo-controlled studies have been published on herbals and other natural supplements as potential treatments of depressed mood, anxiety and other neuropsychiatric symptoms associated with COVID-19 illness; hence, specific treatment recommendations cannot be made. However, as previously noted, numerous clinical trials are ongoing to investigate select natural supplements including vitamin C, vitamin D, zinc, curcumin, omega-3s, probiotics, and NAC (N-acetylcysteine) for promoting immune function, reducing risk of viral infection, and reducing the severity and duration of illness.[34]

In parallel with these efforts, findings of placebo-controlled studies support that select natural supplements have antidepressant effects. Because effects of SARS-CoV-2 on brain function that manifest as neuropsychiatric symptoms are mediated in part by inflammation, natural supplements that have both anti-inflammatory properties and antidepressant effects (eg, vitamin D, zinc, and probiotics) should be investigated as candidates for future treatments of the medical and neuropsychiatric consequences of COVID-19 illness.

Traditional Chinese Medicine

Preliminary findings support the use of select TCM modalities to help reduce symptoms of depressed mood associated with COVID-19. Unfortunately, many TCM approaches used to treat depressed mood lack high quality evidence.[55,56] A review of TCM interventions in patients with COVID-19 (N=972) found evidence that acupuncture, select Chinese herbal medicine, Qigong, and other TCM traditional therapies may improve physical symptoms of COVID-19 illness, including chest pain and impaired respiratory function, as well as psychological symptoms including depressed mood, anxiety, sleep quality.[37] Another study found evidence for use of a combined regimen of auriculotherapy (ie, ear acupuncture) and the Baduanjin style of Qigong for insomnia, depressed mood and anxiety associated with COVID-19.[20] The evidence supporting TCM treatments for depressed mood is inconsistent with findings from some studies on acupuncture and qigong for depressed mood not associated with COVID-19 illness that reported outcomes no better than found with use of placebo.[57,52] Importantly, any consideration of these modalities should include the potential for negative outcomes, and all of these factors must be discussed with patients.

Biofeedback

Various biofeedback approaches are widely used to manage stress and reduce anxiety. Emerging findings suggest that survivors of COVID-19 have autonomic disturbances related to cardiovascular sequelae that can deteriorate in relationship to medical and psychiatric disorders. Heart rate variability (HRV) biofeedback may provide clinically useful information about autonomic disturbances related to COVID-19 illness while potentially decreasing the deleterious impact of cardiovascular, autonomic, physical, and psychiatric sequelae.[58] An ongoing clinical trial aims to determine whether HRV biofeedback reduces anxiety in individuals with long COVID.[59]

It has been suggested HRV biofeedback may be helpful in reducing stress in frontline health care personnel who work with COVID-19 patients; however, this has not been investigated in studies to date.[60] Findings of a small study on (N=55) healthy adolescents during the COVID-19 lockdown suggest that EEG biofeedback training may significantly reduce anxiety, improve mood, and increase emotional resilience.[61-63]

Recommendations

A well-coordinated outreach campaign at the international (ie, WHO) and national (ie, ministries of public health) levels should be aimed at both the general public and health care professionals with the goals of correcting widespread misinformation and false claims about CAM treatments and providing accurate up-to-date information on CAM interventions for enhancing emotional resilience and mitigating psychiatric illness associated with COVID-19 illness. Radical health care reforms (ie, increased reliance on self-directed interventions for enhancing wellness and emotional resilience such as mindfulness, proper nutrition, and exercise) are needed to reduce the economic impact of prolonged lockdowns during future pandemics.

Low-cost mobile applications should be developed to guide the general public in positive lifestyle choices and mindfulness training.[63] Large cohort studies are needed to investigate lifestyle modification approaches (eg, mindfulness, nutrition, exercise, and sleep hygiene) and identify those that optimally enhance resilience for future pandemics and other global crises. Similarly, large, multicenter, placebo-controlled studies are needed to investigate natural supplements (especially those that have both anti-inflammatory and psychoactive properties) as prospective adjunctive or monotherapy treatments of depressed mood, anxiety, and other mental health problems associated with the acute phase of COVID-19 illness and long COVID.

Dr Lake is an adult psychiatrist with more than 25 years of clinical experience. He is an adjunct fellow at Western Sydney University's National Institute of Complementary Medicine Health Research Institute in Penrith, Australia. He founded and chaired the American Psychiatric Association's Caucus on Complementary, Alternative and Integrative Medicine from 2004 to 2010, and has chaired symposia and workshops at American Psychiatric Association conferences and other national and international conferences on complementary, alternative, and integrative mental health care. Dr Lake is the author or editor of 5 textbooks on alternative and integrative mental health care and a 10-volume series of self-help books on alternative and integrative treatments of depressed mood, anxiety, attention-deficit/hyperactivity disorder, bipolar disorder, and other mental health problems.

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POSTTEST, CREDIT REQUEST FORMS, AND ACTIVITY EVALUATIONS

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"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."

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

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

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

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- Relocation assistance may be available

We're also hiring for Staff Psychiatry positions- contact us to learn more!

(916) 654-2609
careers@dsh.ca.gov
www.dsh.ca.gov

DSH California Department of State Hospitals

California

SAN JOAQUIN COUNTY
Greatness grows here.

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


PMPI TeleMed

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.

Income potential of $340-$405K, plus CA Lic, DEA and Malpractice is paid, 1099 income. **Scan QR code to Apply:**

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

IMPERIAL COUNTY
Behavioral Health Services
MENTAL HEALTH & SUBSTANCE USE RECOVERY

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

The Department of Psychiatry at Mass General Brigham Salem Hospital is seeking full-time and part-time BC/BE Adult and Child Psychiatrists to join our growing behavioral health team in Salem, Massachusetts, about 15 miles north of Boston. Salem Hospital is a member of the prestigious Mass General Brigham health care system, and the Department of Psychiatry is closely aligned with the Massachusetts General Hospital , one of *U.S. News & World Report's* top ranked psychiatry programs.

Discover the benefits of being part of our Psychiatry team, including:

- Working at Salem Hospital in the recently opened Epstein Center for Behavioral Health.
- A very reasonable call schedule with additional compensation and no in-house coverage requirements.
- Research and teaching opportunities on-site or at Mass General, Tufts Medical School and Harvard Medical School with possible academic appointment.
- Highly competitive salaries and comprehensive benefits.
- Physician leadership that welcomes input to improve our clinical care, quality and the overall care experience.
- Employee-focused culture that emphasizes physician work/life balance, strives to minimize the stresses of medicine, and allows our providers to find fulfillment.
- Strong mentoring and support for psychiatrists at all levels of experience.
- An outstanding quality of life that comes from living in coastal Massachusetts just 15 miles north of Boston.

WE'RE A BEACON OF NEW THINKING IN INTEGRATED MEDICINE. **JOIN US.**

To apply or learn more about our physician opportunities, visit **joinnspg.org/SpecialtyMedicine**.
Or email your CV and letter of interest to Louis Caligiuri, Executive Director of Physician Recruiting, at **lcaligiuri@partners.org**.

Indiana

INDIANA UNIVERSITY
SCHOOL OF MEDICINE

Staff Psychiatrist
Indiana University School of Medicine
Mental Health Services

The Indiana University School of Medicine Department of Mental Health Services and the Department of Psychiatry is seeking to fill an immediate opportunity for a psychiatrist to join the school and provide clinical care for medical learners and trainees statewide.

The primary role of this position on the mental health services team will be to provide direct clinical care for trainees within the school of medicine including medical students, IUSM graduate students, residents and fellows. This will include clinical evaluation, diagnosis, and treatment of psychiatric disorders and will involve the establishment of treatment goals, treatment planning, medication management, and collaborative work. This position also has the potential to support programming, outreach, and research.

Basic Qualifications: Candidates must possess an M.D. or D.O., have completed a residency in Psychiatry, be board-certified or board-eligible by the American Board of Psychiatry and Neurology, be eligible for licensure in the State of Indiana, and have experience in the delivery of culturally-competent care.

To Apply
Interested candidates should review the application requirements and submit their application at: https://indiana.peopleadmin.com/postings/12769

Questions regarding the position can be directed to Samia Hasan, M.D., hasans@iu.edu

Applications will be considered until the position is filled. Indiana University is an equal opportunity employer committed to building a building a diverse learning environment and on supporting the professional development of ethnic minorities, women, and people with disabilities.

Maryland

PGS
PsychoGeriatric Services

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

New Jersey

SOMERSET COUNTY

Richard Hall Community Health and Wellness Center of Somerset County is an integrated whole-health, progressive behavioral health service provider located in Bridgewater NJ. We are seeking creative, thoughtful and motivated professionals to join our team. Fast-paced, team-oriented environment in which we provide comprehensive care to individuals with mental health and co-occurring substance use and mental health challenges. All positions must be computer proficient as we have an electronic health record. Excellent benefit package and competitive salary. **To apply**: https://www.co.somerset.nj.us/government/finance-and-administrative-services/human-resources/job-posts

Medical Director
28 Hours with benefits
Member of the Executive Management Team reporting to the Executive Director. Has oversight of the medication clinic which provides psychiatric assessment and medication management to Adults, Adolescents and Children. Participates in peer reviews, PI/QA activities, coordinates and supervises the medical practice of the APN's and staff psychiatrists; oversees the compliance of the agency's behavioral health accordance with NJ State DMHAS, Joint Commission and Federal statutory regulation. Works closely with the DON in meeting National Patient Safety Standards of the Joint Commission and updates and writes policy related to all medication clinic related regulations and standards. Carries small case load as needed.

CALL TODAY
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New Mexico

SAN JUAN REGIONAL MEDICAL CENTER

Exciting Opportunity for Psychiatrists in the Beautiful Southwest

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

You can look forward to:

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

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

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

Sage Neuroscience Center

Psychiatric/Addictions Medical Director

Sage Neuroscience Center is a collaborative multidisciplinary clinic for behavioral health, primary care, and addictSageSageions.

The role of Psychiatric/Addictions Medical Director provides leadership in behavioral health collaborating with other clinical and management leaders and reports to the CEO.

Education, Skills, and Experience:

- Board Certified General Adult Psychiatry/ Child and Adolescent Psychiatry. Additional fellowship specialties appreciated.
- 5-10+ years clinical practice experience

TuftsMedicine

Psychiatrists • Eastern Massachusetts

Tufts Medicine is seeking members of psychiatry provider community to join our system of collaborative, compassionate, and impact driven providers. Tufts Medicine includes **Tufts Medical Center, Melrose Wakefield Hospital, Lowell General Hospital** as well as the physicians of the New England Quality Care Alliance. Our behavioral health teams are collegiate, team-based environments with expertise in the care of mental health patients and their families in inpatient, outpatient, addiction, state hospitals and geriatric psychiatric settings. ***Tufts Medicine - as one fully integrated health system, nothing is impossible.***

We offer opportunities across the full spectrum of Psychiatric mental health care to comprehensively take care of our patients and their family's needs. Our current opportunities include, but are not limited to:

- **Addiction Psychiatry**
- **Associate Medical Director**
- **College Health and Wellness**
- **Inpatient Psychiatry at State Mental Hospitals**
- **Medical Director**
- **Outpatient Psychiatry**
- **Transplant Consultation Liaison**
- **Child and Adolescent Outpatient Psychiatry**
- **Consulting Child and Adolescent Psychiatrist**

We encourage you to apply if you are:

- A Board Certified or Board Eligible Psychiatrist
- Interested in academics including an Academic Appointment through Tufts University School of Medicine
- Impact driven and looking to grow within your career
- Dedicated to patient recovery and family support
- Passionate in helping those who suffer mental illness through innovative, respectful, empowering and compassionate care

Please apply online at: clinicalcareers.tuftsmedicine.org
For inquiries please contact: Kathryn.Kull@tuftsmedicine.org

EOE - We warmly welcome all candidates of diverse origin, background, ability, age, sexual orientation, gender identity, and personality.

• 3+ years management experience
• Must be licensed to practice Psychiatry in the state of New Mexico.
• Current DEA certificate
• Excellent communication skills, verbal and written
• Ability to work with others and demonstrate strong leadership qualities
• Spanish-speaking a plus

Compensation:
• Salary commensurate with experience
• 4 weeks PTO
• Malpractice allowance
• Professional development allowance
• Medical, dental, vision coverage
• 401k match

For more information, please contact:
Patti Brammer
pbrammer@sageclinic.org
505-884-1114, ext. 798

We provide the foundation; you build the life. Together, we start the solution.

North Carolina

CAPE FEAR VALLEY HEALTH

We Want You to Join Our Behavioral Health Team!

Cape Fear Valley Behavioral Health is one of the largest comprehensive, multi-tiered behavioral health services in North Carolina. Behavioral Health Care's mission is to meet and respond to the mental health needs of the community. We offer evidence-based, best practice treatments. Staffed by psychiatrists, psychologists, clinical social workers, psychiatric nurses, licensed professional counselors, and other mental health professionals, Cape Fear Valley Behavioral Health Care provides a team approach to mental wellness. Behavioral Health Care is accredited by The Joint Commission and licensed by the State of North Carolina.

The Health System is seeking providers for the following due to regional volumes and commitment to expand services:

Emergency Opportunity
• Two BE/BC providers with experience in ED or trained in ED/Psychiatry. The Emergency Department maintains a Psychiatric Unit of 9 beds for patients in crisis. Support team is specialty trained. Schedule consists of 16 hour shifts, approximately 10 shifts per month.

Adult Outpatient Opportunity
• BE/BC provider with training/experience in a variety of mental health treatment conditions as well as Chemical Dependency and Substance Abuse. Candidate with experience in treatment of Bipolar Disorder, Borderline Personality Disorder, and Mood Disorders is preferred.

Additionally, ECT training and experience is highly desirable. Well established adult team is flexible and transparent for either or both inpatient and outpatient services. Clinic hours are Monday - Friday with limited call

Child Outpatient Opportunity
• BE/BC Child & Adolescent providers. The current structure is for 90% outpatient Monday through Friday work schedule.

We offer best in class compensation plus generous benefits including Paid Malpractice, CME Time and Allowance, Accrued Paid Time Off, 403(b) match and 457(b), Health, Dental, and other desirable benefits.

Please contact Suzy Cobb, Physician Recruiter for more details at (910) 615-1889 or scobb2@capefearvalley.com

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FAMILY PSYCHIATRY PRACTICE & ASSOCIATES

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

to join an established group practice in Cary, NC. Out-patient only, fee-for-service, no managed care, multidisciplinary group with C&A/Adult psychiatrists and psychologists in a family-oriented practice situated in a community consistently rated as one of the top places to live in the country. Minutes from RTP and 3 major universities. Flexibility in job, excellent collections and benefits. For inquiries email CV to Practice Manager jgawdi@fppa.com. Website: www.fppa.com

Oregon

PeaceHealth

Outpatient (FT) & Per Diem Only Positions | Oregon

PeaceHealth is seeking licensed Psychiatrists for full-time and per diem roles in Springfield, OR. Enjoy flexibility and work with a varied and interesting group of patients from children to geriatrics. Our intensive outpatient program & partial hospitalization program offers expanded wrap-around services for young adults. Mentor, teaching and research opportunities available. Be part of a coordinated continuum of care and collaborate with ED and full crisis team. PeaceHealth is a non-profit health system serving the majestic Pacific Northwest.

Contact: Danny Keo, Provider Recruiter
dkeo@peacehealth.org | (971) 404-6681

PeaceHealth

Consult Liaison | Oregon

PeaceHealth is seeking licensed Psychiatrists to join our Consult Service primarily working at PeaceHealth Riverbend Medical Center in Springfield, Or. Working with a varied, interesting & challenging group of patients. Mentor/ teaching and research opportunities. ETC Services available. Build your career in a large, well-respected and established Inpatient and Outpatient Psychiatry group. PeaceHealth is a non-profit healthcare system serving the majestic Pacific Northwest.

Contact: Danny Keo, Provider Recruiter
dkeo@peacehealth.org | (971) 404-6681

PeaceHealth

Child and Adolescent | Oregon

PeaceHealth is seeking licensed Child & Adolescent Psychiatrists for full-time and per diem roles primarily working at PeaceHealth Riverbend Medical Center in Springfield, OR. Enjoy flexibility and work with a varied and interesting group of patients. Mentor, teaching and research opportunities may be available. Be part of a coordinated continuum of care and collaborate with ED and full crisis team. PeaceHealth is a non-profit health system serving the majestic Pacific Northwest.

Contact: Danny Keo, Provider Recruiter
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Psychiatric Times™ classifieds section and job board provides you with the exclusive opportunity to promote your products and services directly in the mental health space.

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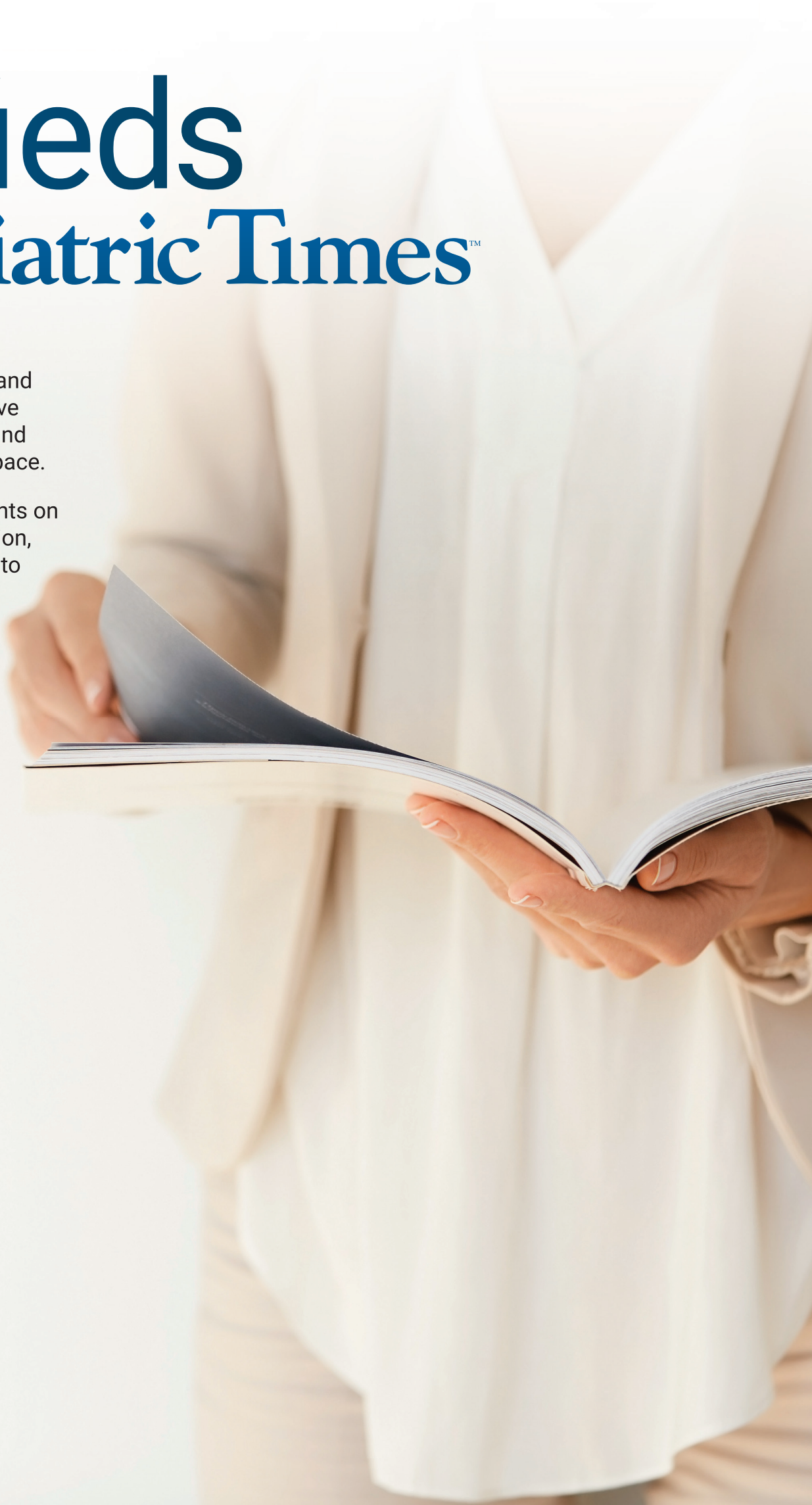

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AN MJH life sciences™ BRAND

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)	
Clinical Implication:	Concomitant use of INGREZZA with MAOIs may increase the concentration of monoamine neurotransmitters in synapses, potentially leading to increased risk of adverse reactions such as serotonin syndrome, or attenuated treatment effect of INGREZZA.
Prevention or Management:	Avoid concomitant use of INGREZZA with MAOIs.
Examples:	isocarboxazid, phenelzine, selegiline
Strong CYP3A4 Inhibitors	
Clinical Implication:	Concomitant use of INGREZZA with strong CYP3A4 inhibitors increased the exposure (Cmax and AUC) to valbenazine and its active metabolite compared with the use of INGREZZA alone. Increased exposure of valbenazine and its active metabolite may increase the risk of exposure-related adverse reactions.
Prevention or Management:	Reduce INGREZZA dose when INGREZZA is coadministered with a strong CYP3A4 inhibitor.
Examples:	itraconazole, ketoconazole, clarithromycin
Strong CYP2D6 Inhibitors	
Clinical Implication:	Concomitant use of INGREZZA with strong CYP2D6 inhibitors increased the exposure (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.
Prevention or Management:	Reduce INGREZZA dose when INGREZZA is coadministered with a strong CYP2D6 inhibitor.
Examples:	paroxetine, fluoxetine, quinidine
Strong CYP3A4 Inducers	
Clinical Implication:	Concomitant use of INGREZZA with a strong CYP3A4 inducer decreased the exposure of valbenazine and its active metabolite compared to the use of INGREZZA alone. Reduced exposure of valbenazine and its active metabolite may reduce efficacy.
Prevention or Management:	Concomitant use of strong CYP3A4 inducers with INGREZZA is not recommended.
Examples:	rifampin, carbamazepine, phenytoin, St. John's wort[1]
Digoxin	
Clinical Implication:	Concomitant use of INGREZZA with digoxin increased digoxin levels because of inhibition of intestinal P-glycoprotein (P-gp).
Prevention or Management:	Digoxin concentrations should be monitored when coadministering INGREZZA with digoxin. Increased digoxin exposure may increase the risk of exposure-related adverse reactions. Dosage adjustment of digoxin may be necessary.

[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).

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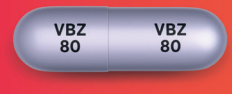
CP-VBZ-US-0203v6 03/2022

ADVERTISEMENT

HELP YOUR ADULT PATIENTS WITH TARDIVE DYSKINESIA (TD)

Take.



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Control.

INGREZZA is the simple, once-daily choice to reduce TD severity[1]

Actor portrayal

THE SIMPLE CHOICE

Once-daily INGREZZA is the simple choice to support patient adherence[1,2,*]

SYMPTOM REDUCTION

INGREZZA 80 mg reduced uncontrolled movements in **7 of 10 patients at 6 weeks** (post hoc analysis)[1,3,†]

SAVINGS & SUPPORT

$10 or less out-of-pocket is what most patients pay for INGREZZA[4]

*Compared to once-daily regimens, timing adherence is 27% lower for twice-daily regimens, according to a meta-analysis of 51 studies in patients with chronic conditions.

†Post hoc analysis included patients who had a baseline and a Week 6 AIMS total score. Reduction in uncontrolled movements as assessed by ≥1-point decrease in AIMS total score.

ONCE-DAILY
INGREZZA®
(valbenazine) capsules

#1 MOST PRESCRIBED TREATMENT FOR TARDIVE DYSKINESIA[5]

Visit INGREZZAHCP.com/Results to see how you can help your TD patients take control

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

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

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

REFERENCES: 1. INGREZZA [package insert]. San Diego, CA: Neurocrine Biosciences, Inc. **2.** Coleman CI, Limone B, Sobieraj DM, et al. Dosing frequency and medication adherence in chronic disease. *J Manag Care Pharm.* 2012;18(7):527-539. **3.** Data on file. Neurocrine Biosciences, Inc. **4.** Data on file as of Q1 2021. Neurocrine Biosciences, Inc. **5.** Data on file as of Q3 2021. Neurocrine Biosciences, Inc.

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