THE PSYCHIATRIC PIPELINE

10 Agents to Watch

>> John J. Miller, MD

Despite a diverse and ever-expanding menu of psychotropic medications, most clinicians still look expectantly down the psychiatric drug pipeline, hoping for novel agents to improve their treatment outcomes for everything from psychosis to depression. The history of psychotropic medication may be full of serendipity and setbacks (Sidebar), but it has included undeniable successes, serving as a powerful ally in our mission to decrease emotional pain and suffering by offering actionable modification of the brain’s architecture.

CONTINUED ON PAGE 6

CLINICAL ANXIETY & STRESS DISORDERS

Post–COVID-19 Stress Disorder: Another Emerging Consequence of the Global Pandemic

>> Phebe Tucker, MD, and Chris Czapla, MD

Throughout 12,000 years of human history, pandemics have killed an estimated 300 million to 500 million people, with the bubonic plague decimating an estimated 60% of the European population during the Middle Ages. Despite modern advances in medicine, coronavirus disease 2019 (COVID-19) has caused more than 1 million reported deaths in less than a year. Aside from the death toll, the pandemic has triggered significant emotional, physical, and economic problems around the world. But even in the midst of this crisis, nations have an opportunity to share and learn from each other’s experiences.

The emerging literature measures the impact of various traumatic events caused by the COVID-19 pandemic. Continued on page 9.
CAPLYTA FOR SCHIZOPHRENIA
IN ADULTS

**Important Safety Information**

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

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

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

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

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

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

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

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

**THIS ISN’T JUST A COFFEE RUN.**
Choose CAPLYTA to help control your patients’ symptoms—with a metabolic, weight, and EPS profile similar to placebo in 4- to 6-week trials.

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

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

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

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

**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.
**INDICATIONS AND USAGE**

CAPLYTA is indicated for the treatment of schizophrenia in adults.

**CONTRAINDICATIONS**

CAPLYTA is contraindicated in patients with history of hypersensitivity reaction to lumateperone, any component of CAPLYTA, or antipsychotics. In such patients, consider discontinuation of CAPLYTA at the first sign of a clinical or allergic reaction. Do not administer CAPLYTA to patients with known or suspected seizure disorders; lumateperone may exacerbate seizures. Use CAPLYTA with caution in patients with a history of increased intracranial pressure or uncontrolled seizures.

**WARNINGS AND PRECAUTIONS**

**Concomitant Use with Antipsychotics**

**Increased Mortality in Dementia-Related Psychosis**

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (median duration of 10 weeks) of antipsychotics in patients with dementia-related psychosis showed a risk of death in 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 the drug-treated patients of between 1.6 to 1.7 times that in placebo-treated patients. Although the causes of death were diverse, most of the deaths associated with antipsychotics were either cardiovascular or respiratory in nature. CAPLYTA is not approved for the treatment of patients with dementia-related psychosis.

**Seizures**

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

**Neuroleptic Malignant Syndrome**

A potentially fatal symptom complex, has been reported in association with administration of antipsychotic drugs. The syndrome is characterized by hyperpyrexia, muscle rigidity, and autonomic instability. Additional signs may include elevated creatinine phosphokinase, myoglobin (rhabdomyolysis), and acute renal failure. The symptoms generally occur during the initial stages of antipsychotic treatment, especially in elderly patients, and tend to be more pronounced at higher plasma levels. The syndrome may also occur after a dose increase or following a missed dose. The symptoms may be reversed by discontinuing the drug and supportive therapy. Treatment should not be resumed at any dose level. CAPLYTA is not approved for the treatment of patients with neuroleptic malignant syndrome.

**Cardiovascular Effects**

Cardiovascular effects have been observed in elderly patients during long-term treatment with antipsychotics, including CAPLYTA. These effects include, but are not limited to, increased blood pressure, elevated heart rate, orthostatic hypotension, and cardiac arrest. CAPLYTA should be used with caution in patients with cerebrovascular disease. CAPLYTA has not been evaluated in patients treated with antipsychotics who have cerebrovascular disease. The cardiovascular effects of CAPLYTA may be exacerbated by concomitant use of drugs that may affect the sympathetic nervous system, such as propranolol, metoprolol, or any other drug that may have an alpha-adrenergic blocking effect. Concurrent use of CAPLYTA with any drug that may cause hypotension should be avoided. It is recommended that CAPLYTA be used with caution in patients who may experience hypotension due to concurrent use of such drugs.

**Concomitant Use of Drugs with Antipsychotics**

**Antipsychotics, including CAPLYTA, may cause somnolence, postural hypotension, and motor and sensory instability, which may lead to falls and, consequently, injuries.** (Table 1).

**ADVERSE REACTIONS**

**Continued**
FROM THE CHAIRMAN

New Beginnings, New Promises

The beauty of a new year is the blank slate it presents. We close the book on the previous year, hopefully wiser from lessons learned, and charge forward expectantly. After last year, such a gift is particularly appreciated.

On that note, *Psychiatric Times* is poised to jump into 2021 with great excitement. John J. Miller, MD, our editor in chief, explores the psychiatric treatments in the pipeline. Some of these agents leverage innovative pharmacology, and all offer the hope of improved outcomes for patients.

We also welcome new Section Editors to *Psychiatric Times*™, Sheldon H. Preskorn, MD, a long-time contributor, now joins us as the Psychopharmacology Section Editor. Dr. Preskorn is a professor in the Department of Psychiatry and Behavioral Sciences at the University of Kansas School of Medicine in Wichita. Also familiar to readers, Rajesh Tampi, MD, MS, DFAPA, chairman of the Department of Psychiatry & Behavioral Sciences at Cleveland Clinic Akron General in Akron, and chief of the Section for Geriatric Psychiatry at Cleveland Clinic, is now serving as our Geriatric Psychiatry Section Editor. As part of our commitment to diversity, Advisory Board member Frank A. Clark, MD, is our new Diversity and Inclusion Section Editor. Dr. Clark is a clinical assistant professor at the University of South Carolina School of Medicine Greenville, and the medical director and division chief for Adult Inpatient and Consult-Liaison Services for the Department of Psychiatry and Behavioral Medicine at Prisma Health. We also welcome Anita H. Clayton, MD, chair of psychiatry and neurobehavioral sciences and the David C. Wilson Professor of Psychiatry and Neurobehavioral Sciences at the University of Virginia School of Medicine, as our Women’s Issues Section Editor. Horacio A. Capote, MD, medical director of the Division of Neuropsychiatry at Dent Neurologic Institute and medical director of addiction services at BryLin Hospital, in Buffalo, New York, will serve as our Neuropsychiatry Section Editor. In our continued effort to address collaboration, we are pleased to have Sara Robinson, MSN, RN, PMHNP-BC, join *Psychiatric Times*™ as Nurse Practitioner Liaison. Ms Robinson is a psychiatric-mental health nurse practitioner in Portsmouth, New Hampshire, and a clinical assistant professor in the Department of Nursing at the University of New Hampshire College of Health and Human Services in Durham.

This year we are excited to highlight contributions from our partner organizations and associations. In this issue, David “Daven” E. Morrison, MD, and colleagues from the Committee on Work & Organizations of the Group for the Advancement of Psychiatry share their thoughts on job loss. Previous *Psychiatric Times*™ articles have elucidated the direct neuropsychiatric implications of coronavirus disease 2019 (COVID-19). In this piece, these authors discuss how COVID-19 affects employment and how psychiatrists can assist their patients who are struggling with job loss.

There is much reason for optimism as we step into 2021: potential new treatments, a COVID-19 vaccine, and renewed hope and enthusiasm. Through it all, *Psychiatric Times*™ is committed to keeping you up-to-date with the latest information and providing you with the resources you need to help your patients. If you have suggestions or requests to better assist you and your colleagues, let us know by emailing PTEditor@psychiatrictimes.com.
n honor of the New Year, I reviewed a list of 10 novel agents in the pharmaceutical pipeline that demonstrate an array of mechanisms that may eventually join our clinical pharmacopeia (see cover story). Several of these agents hold promise as treatments to improve efficacy as well as tolerability for significant subpopulations of our patients. Amidst the excitement and hope of novel drugs, it is important to place our expectations and curative fantasies in the appropriate context. As of today, based on what we know, the human brain remains the most complex organ in the universe. The average adult brain weighs only 3 lbs and is constructed with 80 billion neurons. Each neuron connects to other neurons with up to 10,000 synapses. These synapses are in a constant state of neuroplasticity, strengthening connections here and reducing connections there based on the ever-changing demands of our environment—both internal and external.

Remarkably, each human brain has approximately 1 quadrillion synapses/connections that define our moment-to-moment changing connectome, which is the foundation of our uniqueness and identity. One quadrillion equals 1,000,000,000,000,000,000, which is the number 1 followed by 15 zeroes: wrap your mind around that—pun intended. We continue to discover novel receptors, substrates, genetic polymorphisms, epigenetic modifications, enzymes, neurotransmitters, synergistic/antagonistic interneuronal connections, and more with each passing day. This list is limited to physical elements of the brain that create our current primitive understanding of the nature of consciousness.

Additionally, we are relatively clueless as to the variables that weave together to create a personality, determine how much resilience a person has, or contribute to the opposing qualities of compassion and unprovoked aggression toward others. Nonetheless it is truly remarkable how much we have learned about our brains during the past century. From sequencing the entire human genome, to mapping out neural microcircuits that cross through divergent brain structures, to the windows into brain function that MRI, positron emission tomography, and single-photon emission computed tomography scans have opened, our basic science knowledge of the brain continues to explode beyond what science fiction of the past predicted.

Our basic science knowledge of the brain continues to explode beyond what science fiction of the past has predicted.
creased. The introduction of clozapine to the United States in 1989, our first antipsychotic FDA approved for treatment-resistant schizophrenia, led to a second wave of deinstitutionalization. In my state of New Hampshire, the number of psychiatric patients hospitalized at New Hampshire State Hospital dropped from 2700 in 1963 to 120 in 2013, according to Jay Couture, CEO of Seacoast Mental Health Center, Portsmouth, New Hampshire. Let me be clear, this dramatic decrease in national and NH state hospital admissions is not entirely based on newer or better medications, nor is it necessarily something of pride. On October 31, 1963, President John F. Kennedy signed the Community Mental Health Act into law. He applied our medical knowledge and understanding in a broad and comprehensive intervention that affects many elements of day-to-day life. Here at the beginning of 2021, 30 years after George Bush’s “decade of the brain,” we continue to struggle to achieve adequate response and less commonly full remission in all the major psychiatric disorders. As I see it, we are right where we should be. Progress is always incremental, with an occasional paradigm shift. In psychiatry we have learned that optimal treatment of our patients includes far more than medications, including the drugs in the pipeline. The same can be said about all medical disorders. Despite huge advances in medicine and surgery, illness is a familiar part of most of our lives. We will likely never attain a complete understanding of the human mind, body, and soul. Knowledge is limited by the biases and tools of inquiry that we bring to our exploration of what is not known—which certainly greatly exceeds that which we know. Yet a fascinating quality of us humans is that we act and pretend like we know everything in contrast to the generation that preceded us. In psychiatry we sometimes speak with amusement, condescendence, or disgust when we teach students about the cutting-edge treatments of the mid-1900s. Insulin shock therapy was used routinely during the 1940s and 1950s for the treatment of schizophrenia. Frontal lobotomies were performed during this same time period for a variety of psychiatric disorders; this involved inserting an instrument into the prefrontal cortex and severing neuronal connections, which commonly resulted in a dramatic loss of the individual’s prior personality and intellect. You can be sure that we will be equally judged in 100 years for our current state-of-the-art treatments. The good news is that this is how science and the advancement of knowledge works. In 1675, Isaac Newton wrote in a letter to Robert Hooke: “If I have seen further it is by standing on the shoulders of Giants.” Ultimately, no single person discovers or invents any one thing. Rather, insights organically arise when the necessary foundation has been established by the hypothesis and theories of predecessors, along with an infinite number of unknowable factors that converge to enlighten that moment in time.

Ultimately, we deserve to revel in every scientific breakthrough, no matter how large or small. However, we must remain mindful that today’s treatments will eventually become outdated and replaced by the discoveries of tomorrow, and this is what good science is all about. We must humble ourselves as modeled by one of science’s greatest minds—Isaac Newton: “I do not know what I may appear to the world, but to myself I seem to have been only like a boy playing on the seashore, and diverting myself in now and then finding a smoother pebble or a prettier shell than ordinary, whilst the great ocean of truth lay all undiscovered before me.”

It would be naïve to anticipate that one day we will understand that great ocean of truth, but we should never cease in our curiosity, exploration, and discovery of yet another pebble or seashell.

REFERENCES
The Psychiatric Pipeline

Continued from Cover

Fortunately, there are a number of agents in the current psychiatric pharmacological pipeline (Table). Not only do they offer promise of new treatments to help patients, but they also further our understanding of brain function and dysfunction. The following is a sampling, in no particular order, of drugs in various stages of clinical development.

**Kar-XT: Combination of Xanomeline and Trospium**

The muscarinic cholinergic system has been of interest in psychiatry since the US Food and Drug Administration (FDA) approval of chlorpromazine, which has significant anticholinergic adverse effects. Additionally, 3 FDA-approved medications for the treatment of Alzheimer disease are centrally active acetylcholinesterase inhibitors that increase acetylcholine levels in the brain. There are 5 muscarinic cholinergic subreceptors (M1 through M5), and all are metabotropic. They are in sharp contrast to those in the nicotinic cholinergic receptor family, which are all ion channels.

Xanomeline is a muscarinic M1/M4 receptor-preferred agonist that has demonstrated improvement of both positive and negative schizophrenia symptoms in clinical trials. Theoretically, M1 agonism in the prefrontal cortex improves cognition and negative symptoms, whereas M4 agonism in subcortical areas maintains dopamine homeostasis, which is believed to decrease positive symptoms. In patients who received monotherapy with xanomeline, the drug was poorly tolerated due to the cholinergic adverse effects, including vomiting, nausea, diarrhea, excessive sweating, and salivation.

Trospium is a peripheral muscarinic antagonist that does not cross the blood-brain barrier, and it was added to xanomeline in the combination drug Kar-XT. Recently, the agent demonstrated positive results in a phase 2 trial in schizophrenia, with a reduction in positive and negative symptoms as well as good tolerability.

**SEP-856: TAAR-1 and 5HT1A Agonist**

SEP-856 (also known as SEP-363856) is an intriguing molecule. It has demonstrated efficacy, according to the results of a published phase 2 study of the treatment of an acute exacerbation of schizophrenia. The approximate pretreatment mean baseline Positive and Negative Syndrome Scale (PANSS) score of participants was 100. At week 4, investigators found a 17.2-point decrease in the PANSS for SEP-856 in the active treatment group, versus a 9.7-point decrease in the placebo group. The rates of extrapyramidal symptoms (EPS), change in lipids and hemoglobin $A_{v}$, and prolactin levels in the treatment group were similar to those in the placebo group. A phase 3 study is currently under way.

A significant pharmacodynamic property of SEP-856 is that it demonstrates no activity at any of the 5 dopamine receptors. SEP-856’s mechanism of action can be best understood by reviewing how caffeine indirectly increases dopamine levels in the brain through a receptor complex of 2 different types of receptors known as heterodimers. In the absence of caffeine during the course of the day, the neurotransmitter adenosine increases in concentration and agonizes adenosine receptors, increasing drowsiness. This results directly from the heterodimeric complex of adenosine receptors and dopamine, receptors (D2Rs). As adenosine increases in the brain, it decreases dopamine activation.

Caffeine is structurally similar to adenosine. It functions as a noncompetitive antagonist at the adenosine site of the adenosine-dopamine receptor heterodimer complex. As brain caffeine levels increase, adenosine is displaced from this heterodimer resulting in increased dopamine activity.

Similarly, in the human brain, trace amine-associated receptor 1 (TAAR-1) forms a heterodimer receptor complex with the D2R. TAAR-1 is a G-protein-coupled receptor that functions like a rheostat on the D2R; it is located in brain regions related to the limbic system, reward circuits, cognitive processes, and mood.

Trace amines are endogenous monoamines that are related to dopamine, norepinephrine, and serotonin. The 2 most common trace amines are p-tyramine and 2-phenylethylamine, both of which naturally occur in concentrations 2 orders of magnitude lower than dopamine/norepinephrine/serotonin. Agonism of TAAR-1 by these trace amines decreases dopamine activity, including a decrease in mesolimbic dopamine neuronal firing.

It is hypothesized that SEP-856’s efficacy in improving the PANSS score in individuals with schizophrenia is related to its agonism of the TAAR-1 receptor, which would indirectly decrease dopamine activity. Additionally, SEP-856 agonizes the serotonin 5HT1A receptor, and further research is under way to determine how this mechanism may contribute to improvement in schizophrenia symptoms.

**SAGE-217: Zuranolone**

In 2019, the FDA approved brexanolone (intravenous [IV] allopregnanolone) as a first-in-class medication for the treatment of postpartum depression. Allopregnanolone is an endogenous neuroactive steroid that functions as a γ-aminobutyric acid (GABA) type A receptor positive allosteric modulator. Although its mechanism of action is unknown, allopregnanolone is believed to improve symptoms of depression and anxiety by amplifying GABAergic signaling throughout the brain. GABA is the primary inhibitory neurotransmitter in the brain. When it binds to the GABA-A receptor, there is a resulting influx of chloride ions (negatively charged) into the neuron; this results in a hyperpolarization of that neuron, hence the inhibitory effect.

GABA$_{A}$ receptors have multiple subunits, α 1 through α 6, and various GABA$_{A}$ receptor active drugs bind only to certain subsets of these polymorphic receptors. Examples of other drugs that allosterically activate the GABA$_{A}$ receptors include alcohol, benzodiazepines, and barbiturates. Adverse effects of these drugs include sedation, somnolence, and loss of consciousness. SAGE-217 (zuranolone) is an oral formulation of allopregnanolone currently in clinical trials for postpartum depression, and the treatment of major depressive disorder (MDD) in men and women.

**AXS-05: Combination of Dextromethorphan and Bupropion**

During the 1940s, the US Navy and Central Intelligence Agency funded research to develop a non-

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**Table. A Sampling of Agents in the Psychiatric Pharmacological Pipeline**

| 1 | Kar-XT: Combination of xanomeline and trospium |
| 2 | SEP-856: TAAR-1 and 5HT$_{1A}$ agonist |
| 3 | SAGE-217: Zuranolone |
| 4 | AXS-05: Combination of dextromethorphan and bupropion |
| 5 | AK-831: D-Amino acid oxidase inhibitor |
| 6 | NV-5138: Sestrin modulator |
| 7 | Hydroxymerktamine |
| 8 | Psilocybin |
| 9 | MIN-101: 5HT$_{1A}$ and Sigma-2 receptor antagonist |
| 10 | ALKS 3831: Combination of olanzapine and samidorphan |
addictive synthetic analogue of codeine that could be used as a cough suppressant. Dextromethorphan, the result of this research, was patented in 1949; approved by the FDA in 1954; and approved as an over-the-counter drug in 1958. Dextromethorphan has a complex pharmacology that includes activity as an uncompetitive NMDA-glutamate antagonist; sigma-1 agonism; and nonselective serotonin reuptake inhibition. In 1985, the FDA approved bupropion as the first selective norepinephrine/dopamine reuptake inhibitor. It is currently approved for MDD, seasonal affective disorder, and nicotine dependence. Later it was discovered that bupropion is a potent inhibitor of the cytochrome P450 2D6 (CYP2D6) enzyme, which is the pathway that metabolizes dextromethorphan to dextrophor.

The fixed combination of these 2 old drugs (oral dextromethorphan 45 mg/bupropion 105 mg po twice a day) is AXS-05. Dextromethorphan shares some of the same pharmacological properties as ketamine and its isomers. Prolonging dextromethorphan’s serum level by the potent CYP2D6 inhibition of bupropion, and adding in the norepinephrine/dopamine reuptake inhibition of bupropion, is the putative mechanism of AXS-05’s antidepressant effect.

GEMINI, a phase 3 randomized double-blind, placebo-controlled study in patients with MDD, found AXS-05 improved the Montgomery Asberg Depression Rating Scale (MADRS) score by 4.7 points compared with placebo (P = .002) at 6 weeks (the primary end point). Additionally, at the week 1 key secondary end point, AXS-05 improved the MADRS score by 2.4 points compared with placebo (P = .007).7

TAK-831: D-Amino Acid Oxidase Inhibitor

Life began on Earth approximately 3.5 billion years ago. Amino acids are the building blocks of all proteins in living organisms, and 20 amino acids are used in protein construction in humans. With the exception of glycine (which is achiral) amino acids have a chiral carbon, meaning they are all stereoisomers, often explained as having 2 structurally unique forms that are mirror images of each other. One way to determine the stereoisomer of a particular amino acid is to shine polarized light through it, which will result in the light turning clockwise or counterclockwise (dextrorotation, dextro or D) or counter-clockwise (levorotation, levo or L). When life evolved on Earth, for reasons we do not understand, all structural amino acids in all living systems were the levo isomers.

An evolutionary advantage of this phenomena was the availability of all the D-amino acid isomers for other biological functions. Such is the case in humans, where there are only 2 D-amino acids with a biological function: D-aspartate and D-serine. L-serine exists ubiquitously in humans as a building block in most proteins. The enzyme serine racemase converts L-serine to D-serine in neurons and plays an important role in the agonism of the NMDA glutamate receptor (NMDAR). In order for the ion channel NMDAR to open, 2 glutamate molecules need to be bound to it, as well as either 2 glycine molecules or 2 D-serine molecules.

A Quick Primer on the Serendipity of Psychopharmacological Development

John J. Miller, MD

Those prone to skepticism frequently lament there has been no meaningful progress in treating schizophrenia and affective disorders since the 1950s. Nothing could be further from the truth. Instead, the discovery process has often been the result of serendipity. For instance, in France, the development of the novel antihistamine chlorpromazine was observed to treat psychotic disorders. It ultimately led to the first wave of deinstitutionalization in the United States. Iproniazid, originally developed to treat tuberculosis, became our first antidepressant after it was shown to improve the mood, appetite, and sense of well-being in patients with a serious illness at tuberculosis sanitariums.

Good basic science ultimately determined that dopamine receptor blockade was the mechanism for treating psychotic symptoms. Elevation of the monoamines serotonin, dopamine, and norepinephrine was associated with the improvement of depression.

Seventy years later, most medications we prescribe to treat psychosis and depression continue to target these same neurotransmitter systems. However, it would be naïve to say that we have made no progress. In fact, we have learned a great deal, so much so that it is not possible to teach it all to psychiatry residents during 4 years of post medical school study. (Take but 1 neurotransmitter system and look at what we have learned to date [Table].)

As is the case with good science, when we finally open a trap door to explain or further understand a hypothesis, the answer often includes a house full of hallways, all awaiting further exploration and discovery. Over the decades many pharmacological holy grails have fallen by the wayside: substance P analogues, neuropeptide Y modulators, cannabinoid receptor antagonists, corticotropin-releasing hormone (or factor) receptor antagonists, nicotinic cholinergic α7 agonists, the NMDA allosteric modulator rapastinel, metabotropic glutamatergic receptor (mGlur) 2,3 agonists, and the buprenorphine/samidorphan combination and a host of others. However, these are not failures. Rather, they are contributions to the ever-growing body of knowledge that allows us to further refine our working model of the brain and how the brain interfaces with consciousness.

| Table. Dissecting the Serotonin Neurotransmitter System (the Short List) |
| Serotonin receptors | Metabotropic (G-protein coupled) | 5-HT1, 2, 4, 5, 6, 7 |
| | Ionotropic (ion channels) | 5-HT2 |
| Subreceptors | 5-HT1A, 1B, 1D, 2A, 2C, 5-HT2A, 5-HT2C, 5-HT3 | |
| Inhibitory receptors | 5-HT2 |
| Excitatory receptors | 5-HT2, 3, 4, 5, 7 |
| Genetic polymorphisms of the serotonin receptors and transport pump genes’ promoter sequences | Genetic polymorphisms of the receptors |
| | Genetic polymorphisms of the receptor genes’ and serotonin transport pump genes promoter sequences |
| | Genetic polymorphisms of synthetic and metabolic enzymes for serotonin |
| Epigenetic modifications | Methylation and acetylation to decrease or increase the production of a specific gene product |
| Geography of serotonin system | Gastrointestinal system, brain, platelets |
| | Presynaptic receptors |
| | Postsynaptic receptors |
| | Variability of subreceptor densities in the same neuron |
| | Serotonin neurons post synaptic target |
| | Role of interneurons to change outcome of signal |
| Pharmacological activity of a drug on a serotonin receptor | Agonist |
| | Partial agonist |
| | Antagonist |
| | Antagonist/partial agonist |
| | Inverse agonist |
| | Allosteric modulator |
Significantly, D-serine binds more tightly to the glycine binding site on the NMDAR than glycine itself. The enzyme D-amino acid oxidase metabolizes D-serine to inactive products.

TAKE-831 is a selective and potent D-amino acid oxidase inhibitor, hence it prolongs the activity of D-serine as an agonist at the NMDAR. In the presence of enough glutamate, the end result is increased activity of the NMDAR, which theoretically can improve negative symptoms in schizophrenia as well as treat Friedrich ataxia.9

**NV-5138: Sestrin Modulator**

The protein kinase mammalian target of rapamycin (mTOR) forms part of a protein complex that is responsible for many functions, including cell growth and synaptogenesis. Researchers have hypothesized that several antidepressants, including esketamine/ketamine, increase neuronal levels of mTOR as one of the final actions in a molecular cascade to treat depression. The amino acid leucine activates mTOR Complex 1 (mTORC1) by binding to the upstream regulator sestrin. NV-5138 is a selective small molecule modulator of sestrin, which readily crosses the blood-brain barrier and putatively facilitates sestrin’s activation of the mTORC1, ultimately providing a rapid antidepressant effect through synaptogenesis in the medial prefrontal cortex (mPFC).

In theory, NV-5138 would bypass much of the molecular cascade that is currently necessary to increase brain derived neurotrophic factor (BDNF) and ultimately activate mTORC1, hence providing a more direct path to synaptogenesis. This might result in a targeted response with less adverse effects. A single dose of NV-5138, in the required presence of BDNF, resulted in a rapid and long-lasting antidepressant effect in rats by putatively increasing synaptogenesis in the mPFC.9

**Hydroxynorketamine**

The FDA approval of intranasal esketamine in March 2019 introduced the first nonmonoamine drug into our pharmacopoeia for the treatment of MDD, and it is approved for both treatment-resistant depression in adults and depressive symptoms in adults with major depressive disorder with acute suicidal ideation or behavior. Similarly, IV ketamine has been used off-label for severe depression since the late 1990s. The chemist Calvin L. Stevens, PhD, discovered ketamine in 1962, and the FDA approved the agent in 1970 as a dissociative anesthetic; it is still in common use as such.

Esketamine/ketamine demonstrate antidepressant effects in less than 24 hours. Although their mechanisms of action remain to be elucidated, both likely involve increasing levels of BDNF and ultimately increasing activity of mTOR. mTOR increases protein synthesis at synapses; this in turn increases synaptogenesis, especially in the prefrontal cortex.9 Ketamine is a 50:50 mixture of its 2 enantiomers esketamine and arketamine, both of which are metabolized to hydroxynorketamine. Hydroxynorketamine does not bind to the NMDA glutamate receptor, but rather activates the AMPA glutamate ion channel with downstream effects in increasing BDNF and mTOR. Hydroxynorketamine has demonstrated rapid antidepressant activity in animal models. Since the drug has no abuse potential and no dissociative effects, investigators are studying hydroxynorketamine as a possible ketamine/esketamine alternative.11

**Psilocybin**

Currently, there are 56 psilocybin clinical trials in various stages registered with the FDA.12 These trials are addressing a range of diagnoses, including treatment resistant depression, MDD, obsessive compulsive disorder, anorexia nervosa, migraine headaches, alcohol use disorder, and advanced stage cancer, as well as for pharmacokinetics and functional brain mapping.

Psilocybin is in the class of drugs called hallucinogens, which have been used in religious and spiritual ceremonies throughout the world for thousands of years. In 1938, chemist Albert Hofmann, PhD, working at the Swiss pharmaceutical company Sandoz created lysergic acid diethylamide (LSD). From 1938 until 1966, hallucinogenic drugs, including LSD and psilocybin, were extensively studied in psychiatry. Regrettably, during the early 1960s, Harvard University’s Timothy Leary, PhD, and Richard Alpert, PhD, applied misguided research protocols to study both LSD and psilocybin, and they were ultimately fired from Harvard. Simultaneously, the use of hallucinogens by anti-Vietnam War activists and the highly visible counterculture sullied the reputation of hallucinogens in the United States. Finally, in 1966, laws prohibiting the synthesis, sale, or ingestion of hallucinogens were passed, and in 1970 they became a Schedule 1 drug. Over the past 50 years, the steady undercurrent of hallucinogenic use with numerous individual reports of significant transcendental psychological experiences has resulted in a revival of clinical interest. The political winds may be shifting, too, as voters in the state of Oregon recently approved the use of psilocybin for mental health purposes.9

Clinical trials are still in the early stages, but researchers at prominent universities in the United States and England and around the rest of the world have been captivated by the benefits of psilocybin when used in 1 or 2 sessions in a safe and controlled environment. Robin Carhart-Harris, PhD, head of the Centre for Psychedelic Research, Division of Brain Sciences at Imperial College, London, England, is a leading pioneer in this research, and results of exploratory open-label studies without placebo control groups have demonstrated impressive improvements in patients with treatment-resistant depression.14,15

**MIN-101: Roluperidone—a 5-HT2A and Sigma-2 Receptor Antagonist**

A huge unmet need is novel agents to treat the negative and cognitive symptoms of schizophrenia. All current antipsychotic medications antagonize (through antagonism or antagonism/partial agonism) the D2R. This antagonism of the D2R in the mesolimbic tract seems essential for treating positive symptoms, namely hallucinations and delusions, with this class of drugs. However, this same D2R antagonism in the mesocortical tract likely worsens the negative and cognitive symptoms that are more pervasive in schizophrenia, and these are the symptoms that ultimately contribute more to functional disability than the positive symptoms.

MIN-101 has no affinity to any of the dopamine receptors. It is a novel agent that binds equipotently to the 5-HT2A and sigma-2 receptors (inhibition constants 7.53 nM and 8.19 nM for 5-HT2A and sigma-2 receptors, respectively). A phase 2b clinical trial enrolled 244 patients with schizophrenia whose positive symptoms were considered symptomatically stable by their treating psychiatrist. To be part of the study, patients needed to demonstrate at least moderately severe negative symptoms for 3 or more months. All patients were hospitalized, during which time all psychiatric drugs were discontinued. After at least 5 days, patients were randomized in a double-blind, placebo-controlled design to receive oral MIN-101 32 mg/day, MIN-101 64 mg/day, or placebo in a 1:1:1 ratio for 12 weeks. The primary outcome was improvement at the end of week 12 in the negative factor score from the PANSS (items N1-N4, G5-G8, G13, and G14). Both doses of MIN-101 demonstrated a statistically significant improvement in the PANSS negative factor score as compared with placebo (32 mg/day with P ≤ 0.042 and 64 mg/day with P ≤ 0.004). There was no significant improvement in positive symptoms compared with placebo in either dose.16
Much is known in psychiatry about the 5-HT_2A receptor, and its antagonism of this receptor is an integral property of many of the atypical antipsychotics. In contrast, we know little about the sigma-2 receptor. We await phase 3 trial clinical results to see whether MIN-101 continues to demonstrate improvement in negative and cognitive symptoms in patients with schizophrenia.

**ALKS 3831: Combination of Olanzapine and Samidorphan**

Olanzapine needs little introduction. The FDA approved it in 1996 as the third atypical antipsychotic, following clozapine and risperidone. Olanzapine has garnered many FDA-approved indications for various psychiatric disorders over the past 24 years, and it has become available as a generic medication. Olanzapine has established efficacy, but confers many possible adverse effects, including significant weight gain, hyperglycemia, hyperlipidemia, and sedation (in addition to other common possible adverse effects of antipsychotic medications). Samidorphan is a potent mu-opioid receptor antagonist, similar in pharmacodynamics to naltrexone and naloxone.

ALKS 3831 is a combination of olanzapine and samidorphan developed to reduce the propensity for weight gain from olanzapine monotherapy. The phase 1 proof of concept study was a randomized, double-blind, placebo-controlled proof of concept study to evaluate samidorphan in the prevention of olanzapine-induced weight gain in healthy male volunteers with a stable body weight (body mass index, 18 kg/m² to 25 kg/m²), which compared the change in weight over a 3-week period of time in 4 cohorts: olanzapine 10 mg/samidorphan 5 mg; olanzapine 10 mg; samidorphan 5 mg; and placebo. The primary end point was change in weight at 3 weeks, which was +2.2 kg, +3.1 kg, +0.1 kg, and +0.8 kg, respectively. Phase 3 studies of ALKS 3831 have been completed. In addition, a New Drug Application has been submitted to the FDA for adults with schizophrenia and adults with bipolar I disorder; approval is pending.

**Concluding Thoughts**

This overview of 10 agents in our psychiatric pharmacological pipeline demonstrates the wide range of mechanisms of action currently under investigation. Each of them could add an important novel medication to our clinical psychopharmacological toolbox. These agents draw upon established mechanisms of action, as well as putative mechanisms that remain to be proven as therapeutic advances. Although our current armamentarium of medications is helpful to a subset of patients, it remains suboptimal, leaving many patients in partial remission of their symptoms, or with no improvement at all. We have come a long way since the serendipity of drug discovery in the 1950s. Sometime in the future we will look back at our current treatments as outdated, and some of them will have been discarded. Not because they never worked, but because the new options are more effective.

**Dr Miller is a director, Brain Health, Exeter, NH; editor in chief, Psychiatric Times**; staff psychiatrist, Seacoast Mental Health Center, Exeter, New Hampshire; consulting psychiatrist, Exeter Hospital, Exeter; consulting psychiatrist, Insight Meditation Society, Barre, Massachusetts.

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and 18.2% poor sleep quality.

Other international studies have examined stress responses in health care workers treating patients with COVID-19. A study of 900 health professionals caring for hospitalized patients with COVID-19 in Singapore and India found relatively low symptoms of anxiety (15.7%), depression (10.6%), and stress (5.2%).

However, among health care workers reporting these issues, more than half had symptoms in the moderate to extremely severe range. In addition, 67% of respondents reported physical symptoms, especially headache, lethargy, anxiety, and insomnia, suggesting somatic expressions of distress. United Kingdom military health care workers were assessed for the effects of inadequate safety equipment on their mental health during the COVID-19 medical response. Those with inadequate equipment had greater odds of having common mental health disorders (2.49), PTSD (2.99), poorer global health (2.09), and emotional problems (1.69).

Only a few studies of mental health problems among patients hospitalized with COVID-19 have been published, with more to come. A study of hospitalized but stable patients found a high prevalence of PTSD (96.2%). A chart review of hospitalized patients with COVID-19 in Spain found more than half of the 841 patients hospitalized with COVID-19 had a neurological symptom. Of these, nonspecific neurological symptoms were identified, as well as disorders of consciousness (19.6%), mostly in elderly patients and in those with severe COVID-19 disease; myopathy (3.1%); dysautonomia (2.5%); and other less frequent symptoms. Neuropsychiatric symptoms were reported by 19.9% of these patients, including insomnia, anxiety, depression and psychosis; these were not associated with disease severity.

Some studies have drawn inferences based on other severe respiratory viruses. A meta-analysis of long-term clinical outcomes for survivors of adult severe acute respiratory syndrome (SARS) and Middle East Respiratory Syndrome (MERS) who were in the intensive care unit (ICU) revealed PTSD prevalence in 39%, depression in 33%, and anxiety in 30% beyond 6 months after discharge, as well as reduced lung function and reduced exercise capacity. Italian experts also concluded that we might anticipate similar outcomes in survivors of COVID-19.

Acute respiratory distress syndrome (ARDS) in ICU survivors of COVID-19 may occur, with an expected survival rate of approximately 25%. Survivors of ARDS may experience persistent fatigue and poor exercise tolerance, pain and weakness, neurological sequelae, and the psychological effects of prolonged ICU stays, as noted in patients with MERS and SARS. Stressors included immobility, separation from family and friends, prolonged sedation, anxiety about health conditions and survival, and subsequent job loss. The authors emphasized the need to identify PTSD (anticipated in up to 30% of ARDS survivors) and other mental health problems, and to provide appropriate and timely multidisciplinary therapy that should continue after discharge. A literature review of studies linking panic disorder, as patients who had SARS suggested that aggravation of panic attacks is highly likely in survivors of COVID-19 in the face of prominent respiratory symptoms, as panic may be triggered by fear conditioning to abnormal breathing problems. The authors urged monitoring for panic as well as obsessive compulsive disorder, PTSD, and generalized anxiety disorder.

Exposure to Nontraumatic Stress

Some mental health care advocates believe the general population may be suffering from various levels of vicarious traumatization, although strictly speaking this would not qualify for PTSD’s Criterion A for trauma exposure. Along these lines, in August 2020 the CDC published results of a large US web-based survey of more than 5000 adults (Table), in which 40.9% endorsed at least 1 adverse mental or behavioral health problem related to the pandemic. Symptoms of a trauma- and stressor-related disorder were reported by 26.3%, symptoms of anxiety or depression by 30.9%, substance use to cope by 13.3%, and serious consideration of suicide in the prior days by 10.7%. Suicidal ideation was significantly higher for younger respondents aged 18 to 24 years (25.5%), minority groups (Hispanic individuals, 18.6%; Black individuals, 15.1%), nonpaid caregivers for adults (30.7%), and essential workers (21.7%). The authors stressed the need to identify at-risk individuals to develop policies to address health inequities, and to increase resources for identifying mental health problems and offering new treatment options, including telehealth treatments.

"In a study of home-quarantined youth in China during the first month of the COVID-19 outbreak, 12.8% had PTSS levels consistent with PTSD."

In a study of home-quarantined youth in China during the first month of the COVID-19 outbreak, 12.8% had PTSS levels consistent with PTSD, with PTSS and distress associated with negative coping styles. Symptom levels were expected to increase with time as quarantine continued. This is important since a formal diagnosis of PTSD requires symptoms to persist for more than a month.

In another online survey conducted early during the Wuhan outbreak, researchers looked at anxiety and depression symptoms (rather than specific PTSS) in relation to social media exposure (SME) to COVID-19 news. The study, which included approximately 5000 adults in China, found high SME was positively associated with higher odds of anxiety and a combination of depression and anxiety, compared with low SME. A longitudinal survey of the general population in China during the initial outbreak, and again 4 weeks later, found the mean Impact of Events Scores to be above the cutoff scores for PTSD symptoms at both times, with moderate to severe stress, anxiety, and depression levels.

Results of an Italian cross-sectional, web-based survey showed a relatively high percentage (29.5%) of PTSS related to the pandemic, suggesting that the pandemic itself could be considered a traumatic event. Similarly, an online survey of almost 3500 people in Spain found symptoms of PTSS (15.8%), depression (18.7%), and anxiety (21.6%), with loneliness the strongest predictor of symptoms. Other factors associated with these problems were female gender, previous mental health or neurological problems, having physical symptoms similar to those of COVID-19, or having a close relative infected.

Nursing home residents have been particularly vulnerable to poor health outcomes; early in the COVID-19 pandemic many facilities adopted strict lockdown policies. However, social isolation is particularly detrimental to the elderly, who may have increased risk for depression, anxiety, worsening dementia, and even earlier death. Given these issues, the Centers for Medicare and Medicaid Services (CMS) recommended safe communal activities for locked-down nursing homes.

In Canada, researchers explored prenatal maternal distress before and during the COVID-19 pandemic. Women assessed during the pandemic had higher levels of depression and anxiety, with levels more likely to be clinically significant, compared with women assessed before COVID-19. During the pandemic, dissociative and PTSD symptoms and negative affectivity were...
also greater, underscoring the need to carefully assess pregnant women to help prevent negative, stress-related outcomes in mothers and infants. Perhaps not surprisingly, when compared with a control population, psychiatric inpatients in China had more PTSD, anxiety, and depression symptoms; more anger, impulsivity, and worries about health; and intense suicidal ideation. Hospitalized psychiatric patients and their mental health caregivers are at high risk for COVID-19 infection, compounding their existing stress. This was noted early in February 2020 in Wuhan, when the virus was diagnosed in at least 50 inpatients with psychiatric disorders and 30 mental health professionals. Factors included lack of protective gear and difficulties isolating. Outpatients with psychiatric disorders are also vulnerable to emotional distress during a pandemic. An online survey of more than 2000 outpatients in China discovered that 20.9% of patients with preexisting psychiatric disorders and 30% of mental health professionals. Factors included lack of protective gear and difficulties isolating.

Outpatients with psychiatric disorders are also vulnerable to emotional distress during a pandemic. An online survey of more than 2000 outpatients in China discovered that 20.9% of patients with preexisting psychiatric disorders had seen their symptoms get worse during the pandemic.

Interventions
How can we help individuals whose mental health has been harmed by COVID-19?

To support medical caregivers assigned to the front line during the pandemic, experts advise addressing burnout, as prolonged efforts may overlap and lead to acute stress disorder and PTSD. Suggestions have ranged from practical measures (such as ensuring adequate PPE, handwashing, and decontamination of surfaces) to developing personnel policies that reassign at-risk medical personnel away from high-risk sites, ensure the safety of their family members, and stress the importance of self-care. Also recommended is providing health care workers access to child care services during expanded work hours and school closures. Workers should have adequate rest and breaks, be excused from less-essential tasks, and have regular information and feedback sessions with managers and the community. In many areas, hospitals provide telephone hotline teams trained to provide psychological assistance. Professional organizations offer physician wellness programs to provide free, confidential sessions to deal with burnout, adjustment problems, family issues, and other mental health sequelae.

The increasing numbers of people who were seriously ill with COVID-19 should be assessed for physical symptoms of chronic pain, with physical therapy and medications adjusted to avoid opioid dependence. Survivors of ARDS should receive evidence-based medications, cognitive behavioral therapy, and other psychotherapies for PTSD, panic, depression, and other mental disorders.

To combat isolation among locked-down nursing home residents, CMS recommends safe communal activities such as book clubs, movies, bingo, and outdoor family visits (ie, on lawns or in parking lots) with precautions of social distancing and PPE. Some nursing homes have provided live music, parades, therapy animals, recordings and photos of loved ones, physical contact with loved ones through plastic protective barriers, and even physical and occupational therapy sessions held outdoors.

Psychological first aid provided by trained community personnel might help the general population as they experience distress during the COVID-19 pandemic. For individuals enduring fallout from personal stressors, experts have recommended expanded use of telehealth to identify and treat mental health conditions, including depression, PTSD and other trauma-related disorders, substance use disorders, and suicidal ideation. Self-help groups, 12-step programs, spiritual and religious services, interest groups, and employee groups working from home are all increasingly using interactive internet-based platforms. And it is essential for societies to provide citizens with assistance for jobs, housing, food, medical care, education, internet connections, and many other basic survival needs.

The current international pandemic and possibly future ones will challenge us and give us the chance to continue to learn and share with one another, hopefully linking us cooperatively rather than polarizing us.

Dr Tucker is professor and vice chair of education, Department of Psychiatry, University of Oklahoma Health Sciences Center, Oklahoma City, OK. Dr Czapla is assistant professor and residency training director, Department of Psychiatry, University of Oklahoma Health Sciences Center, Oklahoma City, OK. The authors have no relevant financial interest.

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The Promise and Potential of Emergency Psychiatry

Scott Zeller, MD

Happy 40th birthday to emergency psychiatry! Many in our field point to a seminal article by Samuel Gerson, PhD, and Ellen Bassuk, MD, in the American Journal of Psychiatry in 1980 as first truly defining the subspecialty of emergency psychiatry. Since those days, we have seen impressive growth, scholarship, diversification, and impact throughout our area of care, and we can confidently state that at 40 years young our subspecialty has never been stronger.

Emergency psychiatry was preceded by the rise of emergency medicine, which became a distinct specialty in the late 1960s, and although a few years behind, emergency psychiatry has paralleled emergency medicine’s long-term development in many ways. Indeed, with overlaps in our patient populations, the fields often intersect and can be complementary. Recognizing this, the practitioners of emergency medicine may be some of emergency psychiatry’s biggest advocates. An emergency medicine physician has even served as the president of the American Association for Emergency Psychiatry (AAEP).

In addition to the AAEP, emergency psychiatry also boasts a major annual conference dedicated to the field, the National Update on Behavioral Emergencies (NUBE). There are emergency psychiatry fellowships offered at multiple medical teaching institutions. Research efforts around the facets of the subspecialty abound, including labs with professors focused solely on behavioral emergencies, and there are numerous textbooks available covering all aspects. And it is now quite common to see young psychiatrists pursuing a career in emergency psychiatry.

Meanwhile, emergency psychiatry programs in all sizes and shapes are now found across the nation and in many foreign countries. They help to improve the care, timeliness, and access to more therapeutic environments, along with trained personnel, for patients that traditionally were held in medical emergency departments (EDs) for long hours waiting for a psychiatric inpatient bed. With the number of behavioral emergency chief complaints now estimated to be 1 in every 7 patients presenting to US EDs, the demand for these programs cannot be understated. Although Emergency psychiatry facilities go by many names, including CPEP (Comprehensive Psychiatric Emergency Program), PES (Psychiatric Emergency Services), EmPATH (Emergency Psychiatry Assessment, Treatment and Healing unit), they have demonstrated the ability to safely stabilize and discharge in less than 24 hours 75% or more of patients previously thought to need inpatient admission. These sites can provide immediate, compassionate, and effective care for many individuals, while also preserving the limited psychiatric inpatient beds for those who truly have no alternative.

Over the last year, we have seen enormous behavioral health impacts not only from the pandemic itself, but also from the stress of lockdowns, isolation, job insecurity, family dynamics, and loss of support networks. Last summer, the Centers for Disease Control (CDC) reported substantial increases in suicidal thoughts and substance abuse throughout the country. Shockingly, 11% of the CDC survey respondents reported suicidal ideation in the previous month, and for young adults aged 18 to 24 years, the number considering suicide jumped to an alarming 25%. Meanwhile, 2020 also opened many eyes to law enforcement’s role with behavioral crisis intervention, suggesting mental health professionals might be better suited for these tasks. Clearly, emergency psychiatry as a discipline will need to climb to even higher levels to assist in these considerable and impactful issues.

However, the road to positive change is not without its obstacles. Despite constituting such a large percentage of their trainees’ future patients, only about 25% of emergency medicine residencies provide formal in-training in acute psychiatric management. Many psychiatry residencies provide only minimal emergency psychiatry experience and education. Still, in too many hospitals, the default treatment for acute patients with acute psychiatric disorders remains little more than heavy sedation and physical restraints.
Given these challenges, how do we leverage the 40 years of advancement in emergency psychiatry to meet the myriad and growing demands of today, and continue to rise to the next level? Here are a few suggestions:

1. Begin the process of making emergency psychiatry an accredited, boarded subspecialty under the Accreditation Council for Graduate Medical Education (ACGME). Emergency psychiatry now meets the same standards and requirements for a psychiatry subspecialty as did consultation-liaison psychiatry, when it was formally recognized in 2005. An accredited subspecialty will be much more formidable in promoting appropriate care, and its tenets more difficult to overlook, even in peripheral training programs and outmoded hospitals.

2. Emergency psychiatry must further deepen its integration with emergency medicine and other adjacent specialties. Behavioral emergencies are encountered in all types of clinical settings by many different types of practitioners, and we must raise awareness with all health care professionals about our capabilities and innovative solutions.

3. We must educate our acute care health systems about the financial benefits of our programs and interventions. For example, a recent study published in the journal Academic Emergency Medicine demonstrated that a psychiatric emergency unit dramatically increased revenue for the affiliated medical ED, while providing better and more prompt care for behavioral emergency patients.1

4. Recognize that according to federal law, psychiatric emergencies are legally equivalent to medical emergencies, with the requirement of hospitals providing the same level of assessments and stabilizing efforts for patients as they would for those with chest pain or having experienced a car accident. We must stop thinking of a false dichotomy between the brain and the rest of the body. Mental health and physical health are completely intertwined, and should not be divided up and treated separately.

5. We need to promote a culture that eliminates the stigma of serious mental illness, while understanding that the symptoms of acute psychiatric illness can be just as painful and debilitating as broken bones and bleeding cuts. Patients who experience auditory hallucinations commanding them to hurt themselves or others are in extreme distress, as are those who are despondent and suicidal. Thus, they should not be rated as a low priority in emergency settings. We must send the message that psychiatric emergencies are as random as any other emergency; people do not plan to become suicidal any more than they would schedule themselves to have a heart attack. Life events are almost always unpredictable, so suggestions that we should plan services to try to catch a psychiatric emergency days before it happens will be about as successful as guessing tomorrow’s lotto numbers. Instead, we should be better prepared for all emergencies, and realize they will not cease any time soon, despite any bureaucrats’ assertion to the contrary.

Emergency psychiatry as its own field holds incredible promise, on top of an already remarkable short history. In the special articles of this month’s Psychiatric Times™, I trust you will see some of that for yourself.

Dr Zeller is vice president for acute psychiatry with the physician partnership Virtuity and assistant clinical professor of psychiatry, University of California, Riverside. He is an Editorial Board Member of Psychiatric Times™.

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The Field as a Master Class in Interviewing

Tony Thrasher, DO, DFAPA

“It is a capital mistake to theorize before one has data. Insensibly one begins to twist facts to suit theories, instead of theories to suit facts.” —Arthur Conan Doyle, “A Scandal in Bohemia”

As the fictional detective Sherlock Holmes notes, the pursuit of truth and facts is not one to be taken lightly. In the field of medicine, the topic of diagnostics is perpetually under pressure to evolve and surpass past performances.

In psychiatry, the idea of diagnostics, assessment, and prognosis has a long history that many have categorized, debated, and (to this day) reviewed.2 However, unlike our peers in other medical specialties, we do not have the luxury of the full use of computed tomography or tissue biopsy. Instead, our best analogue to the things which are conceivable the things which are really mere commonplace of existence.” —Arthur Conan Doyle, "The Adventure of the Bruce-Partington Plans"

In emergency psychiatry, one must conduct an interview while managing efficiency, acuity, and extensive medical complications. As such, it is an area where maintaining a broad medical proficiency is paramount, and this it goes far beyond the crucial understanding of medical stabilization processes (ie, medical clearance).3 Once an individual has been cleared for further psychiatric care, many items pertaining to the patient’s chief complaint and ongoing medical comorbidities are a focus during the emergency interview. How a physician uncovers those items plays a primary role in the successful of the psychiatric intervention.

The emergency psychiatrist must not only maintain a broad medical understanding, but also be skilled and comfortable with a wide degree of risk tolerance and mitigation strategies. The most familiar risks often pertain to suicide and homicide; however, there are a plethora of risk items that must be addressed in every crisis interview. A nonexhaustive list is in the Table.4

The third leg of the tripartite successful psychiatric interview includes multitasking and time management (Figure). Unlike in other interview milieus, these assessments cannot usually be deferred, delayed, or done in a preliminary fashion.

These interviews are often performed in contexts that are complex in terms of acuity, physical plant, and medicolegal stakes. The emergency psychiatrist’s decisions do not occur in a vacuum nor do they go unnoticed, unnoticed, or without scrutiny. There are many shareholders, and, as such, the psychiatric interview is of great complexity when noting the relationships considered. Rather than viewing this through a patient-physician scope, the
emergency psychiatry interview requires broadening that aperture to a patient-physician-family-advocate-guardian-law enforcement-case worker-community individual-probate court lens.

Now, noting that the emergency interview requires sophistication in medical care, risk management, and timeliness, it is also worthwhile to remark how this master class in interviewing attends not only to diagnostics, but also to therapeutics and treatment.

Building Rapport
“The world is full of obvious things which nobody by any chance ever observes.” —Arthur Conan Doyle, *The Hound of the Baskervilles*

A skilled psychiatric interview can function as both treatment and assessment, especially in an emergency psychiatric situation. The clinician must establish immediate, and effective rapport, master service recovery, and appreciate the finer points of psychodynamics in the interview process.

One of the greatest challenges of a complex emergency psychiatric interview is that it may be the psychiatrist’s only chance to ever interact with the patient. As such, the stakes are high, the room for error diminished, and the overall emotional valence to patient and loved ones quite accentuated. The most gifted emergency department interviewers are able to establish rapport in a sincere, direct manner that can reach those in crisis on their darkest days. Not only will this rapport help in lessening a patient’s agitation, but the intervention leads to an enhanced accuracy of whatever information is obtained, as well as to patient satisfaction. A successful emergency interview, consequently, will have tenets of trauma-informed care, patient-centered processing, and autonomous medical decision as core competencies.

Occasionally, when you are dealing with patients during their most difficult times, they will be upset regardless of your intentions. Consequently, the emergency psychiatric interviewer must be aware of and accept advanced service recovery techniques. A patient’s recovery may actually be due to something that occurred in your setting or, more commonly, to events that preceded their arrival. This would include patients who were conveyed to your setting involuntarily and/or those not engaging in the interview as the primary requestor of services.

In the overall field of crisis services, success also highlights the importance of redressing grievances or concerns in the moment. Redressing grievances will assist not only with patient satisfaction, but also with patient loyalty and trust over time. Marketing data indicate that users of a service are often more impressed when a provider deals with an issue successfully, as opposed to when an issue never presents itself.

Although the acuity and speed of the psychiatric emergency settings tend to focus on the biological components of medical research, there are many important aspects to the psychiatric interview rooted in psychodynamic theory. Aside from the rapport, the physician has to fully contextualize the transference and countertransference to successfully engage the patient in a way that benefits both patient and examiner. Additionally, the defense mechanisms noted in a crisis are of priceless significance when trying to navigate items that are lacking in possible nudity but also varying degrees of neuroticism. Once the clinician has moved into the deeper stages of the interview, using techniques pertaining to neutrality, observation, clarification, and confrontation is also beneficial.

Collaboration
“My mind rebels at stagnation.” —Arthur Conan Doyle, *The Sign of Four*

As one can see, the master class in emergency psychiatric interviewing has components of core skills—medical knowledge, risk assessment, efficient multitasking—as well as techniques that lead to beneficial outcomes for all involved—service recovery, dynamics, rapport establishment.

The unique challenges to interviewing in these contexts are the varied stakeholders, laws, and tenets that one must juggle, maintain, and provide quality service toward. To be successful in this arena, one must have proficient communication skills regarding, for example, handoffs with emergency medicine, pediatrics, hospitalists, internists, and/or surgical specialists, as well as when dealing with allied health care colleagues and the lay population. To put a finer point on this, there could be individual patient cases in which the emergency psychiatrist must not only conduct an efficient assessment but also specify the findings to multiple individuals with differing communication needs.

Imagine you are working with a young patient showing signs of psychosis for the past 6 weeks. Your initial assessment appears to rule out medical- or substance-induced etiologies, and the overall clinical picture appears to support the onset of a new primary psychotic disorder. Next steps may include communicating with the patient and their family regarding what this means, while balancing civil rights and the topic of voluntary vs involuntary care. Furthermore, you then need to process engagement, consent, and the desire for long-term treatment. Finally, you need to consider differing styles and options while reaching out to inpatient units for possible admissions. You may be chatting with a variety of personnel when trying to enroll the patient in a first episode psychosis intense outpatient program.

At the rather loud nursing station, you receive calls from the law enforcement group that brought in neighbors involved in past crisis episodes. As you think you are finally settling down to compose your note in the electronic health record, you receive a final request from the training medical student about a discharge readiness checklist and/or restraining orders from neighbors involved in past crisis episodes. As you think you are finally settling down to compose your note in the electronic health record, you receive a final request from the training medical student about a discharge readiness checklist and/or restraining orders from neighbors involved in past crisis episodes. As you think you are finally settling down to compose your note in the electronic health record, you receive a final request from the training medical student about a discharge readiness checklist and/or restraining orders from neighbors involved in past crisis episodes.

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CAHOOTS: A Model for Prehospital Mental Health Crisis Intervention

» Ben Adam Climer, Brenton Gicker

CAHOOTS (Crisis Assistance Helping Out On The Streets) is a mobile crisis-intervention program that was created in 1989 as a collaboration between White Bird Clinic and the City of Eugene, Oregon. Its mission is to improve the city’s response to mental illness, substance abuse, and homelessness.

CAHOOTS is operated by White Bird Clinic, which was formed in 1969 by members of the 1960s countercultural movement. They were interested in alternative and experimental approaches to addressing societal problems. Today, White Bird Clinic operates more than a dozen programs, primarily serving low-income and indigent clientele.

The CAHOOTS model was developed through discussions with the city government, police department, fire department, emergency medical services (EMS), mental health department, and others. The name CAHOOTS is based on the irony of White Bird Clinic’s alternative, countercultural staff collaborating with law enforcement and mainstream agencies for the common good.

When it began, CAHOOTS had very limited availability in Eugene. It has grown into a 24-hour service in 2 cities, Eugene and Springfield, with multiple vans running during peak hours in Eugene. The program—which now responds to more than 65 calls per day—has more than quadrupled in size during the past decade due to societal needs and the increasing popularity of the program.

Programs based on the CAHOOTS model are being launched in numerous cities, including Denver, Oakland, Olympia, Portland, Maine, and others. Federal legislation could mandate states to create CAHOOTS-style programs in the near future. (Senators Ron Wyden of Oregon and Catherine Cortez Masto of Nevada have proposed a bill that would give states $25 million to establish or build up existing programs.)

How Does It Work?

When CAHOOTS was formed, the Eugene police and fire departments were a single entity called the Department of Public Safety. CAHOOTS was designed to be a hybrid service capable of handling noncriminal, nonemergency police and medical calls, as well as other requests for service that are not clearly criminal or medical.

Eugene’s police and fire departments eventually split. CAHOOTS was absorbed into the police department’s budget and dispatch system. It continues to respond to requests typically handled by police and EMS with its integrated health care model.

CAHOOTS operates with teams of 2: a crisis intervention worker who is skilled in counseling and de-escalation techniques, and a medic who is either an EMT or a nurse. This pairing allows CAHOOTS teams to respond to a broad range of situations.

“`If an individual is feeling suicidal and they cut themselves, is the situation medical or psychiatric?”`

For example, if an individual is feeling suicidal and they cut themselves, is the situation medical or psychiatric? Obviously, it is both, and CAHOOTS teams are equipped to address both issues. Typically, such a call involving an individual who engaged in self-harm would result in a response from police and EMS. This over-response is rarely necessary. It can also be costly and intimidating for the patient. They are not criminals, and their wounds are often not serious enough to require more than basic first aid in the field. These patients are usually seeking help, and a CAHOOTS team is trained to address both the emotional and physical needs of the patient while alleviating the need for police and EMS involvement. If necessary, CAHOOTS can transport patients to facilities such as the emergency department, crisis center, detox center, or shelter free of charge.

CAHOOTS is contacted by police dispatchers. If you call the nonemergency police line or 911 in the cities of Eugene or Springfield, you can request CAHOOTS for a broad range of problems, including mental health crises, intoxication, minor medical needs, and more. Dispatchers also route certain police and EMS calls to CAHOOTS if they determine that is appropriate.

CAHOOTS, to a large extent, operates as a free, confidential, alternative or auxiliary to police and EMS. These services are overburdened with psych-social calls that they are often ill-equipped to handle. CAHOOTS staff rely on their persuasion and de-escalation skills to manage situations, not force. Only in rare cases do CAHOOTS staff request police or EMS to transport patients against their will.

A Backup Plan

If a psychiatrist or other mental health provider in the Eugene/Springfield area is concerned about a patient, they can call CAHOOTS for assistance. This usually results in a welfare check.

Let us say, hypothetically, that you are concerned about a patient with bipolar disorder. After a lengthy period of stability, they have been complaining to you that they feel like their prescribed medication is no longer working effectively. You begin receiving phone messages and emails from them consisting of fanatical rantings and incoherent gibberish.

You are concerned, but it is not so severe that you feel compelled to call the police. Perhaps you are reluctant to call law enforcement for a variety of reasons. What do you do? You call CAHOOTS.

Having responded to a similar scenario recently, let me describe what occurred. The patient, although not expecting us, welcomed our response. They explained to us that they felt like their medication was ineffective, and, after days of mania, they were feeling depressed and suicidal.

The patient recognized their own decompensation, and eagerly accepted transport to the hospital. Their mental health care provider was informed that we were transporting them and called the hospital to provide additional information.

We transported the patient to the hospital, and they were admitted to the inpatient psychiatric unit for stabilization. Collaboration between prehospital, hospital, and outpatient services facilitated that incident as smoothly as possible.

Barriers and How to Help

Prehospital mental health crisis response is underdeveloped. Most often, police and EMS are the only options. In some cities, clinicians with masters or doctoral degrees are sent with first responders. Unfortunately, the supply of these clinicians is not enough to meet the demand, but does it need to? Ambulances do not staff medical doctors. Why should prehospital mental health care require masters/doctoral level licensed clinicians? Telepsychiatry services, while important, are no substitute for direct human contact, especially given that some patients will need to be transported to a higher level of care and many do not have the means or ability to participate in telehealth services (because of lack of capacity or lack of resources).

The biggest barrier to CAHOOTS-style mobile crisis expansion is the belief that without licensed clinicians and police, prehospital mental health assistance is ineffective and unsafe. If psychiatrists want a program like this in their area, they can help by using their considerable authority to assure the community that response teams like CAHOOTS can work. Because of their direct lines of communication to the police and familiarity with police procedures, CAHOOTS staff are able to respond to high acuity mental health crisis scenarios in the field beyond what is typically allowed for mental health service providers, which often facilitates positive outcomes and can even prevent deadly outcomes. Their support is vital for program success.

Mr Climer worked for CAHOOTS as a crisis worker for 5 years and an EMT for 2.5 of those years. He now lives in Pasadena, CA where he helps Southern California cities develop CAHOOTS-style programs. Mr Gicker is a registered nurse and emergency medical technician who has worked for CAHOOTS since 2008.

REFERENCES

WHAT DO YOU THINK? SEND COMMENTS TO PTEDEITOR@MHMGROUP.COM.
Benzodiazepine Use and the Risk of Dementia

Rajesh R. Tampi, MD, MS, DFAAPA, DFAAGP, and Adriane Bennett, PhD

Available evidence indicates that benzodiazepines are commonly used to treat various disorders including anxiety, insomnia, agitation, alcohol withdrawal, and seizures. The prevalence of benzodiazepine use among older adults in the United States is approximately 8.7%, but it has been noted that approximately 44% of the prescriptions for benzodiazepine among older adults are potentially inappropriate. The 2019 American Geriatrics Society Beers Criteria identifies benzodiazepines as potentially inappropriate medications for use among older adults. Factors associated with long-term use of benzodiazepines include the following: female sex, a diagnosis of Alzheimer disease (AD), schizophrenia, bipolar disorder, depression, coronary artery disease, and asthma/chronic obstructive pulmonary disease.

Consequences of Benzodiazepine Use

The use of benzodiazepines is known to be associated with poor outcomes. One study found that benzodiazepine use was associated with greater risk for hospitalizations, emergency department visits, outpatient visits, and higher health care costs. Another study found the overdose death rate increased due to benzodiazepine use from 0.58 to 3.07 per 100,000 adults between 1996 and 2013. Benzodiazepine use is also associated with an increased risk of falls among older adults. Additionally, the use of benzodiazepines is associated with a 60% to 80% increase in the risk of traffic accidents. The co-ingestion of benzodiazepines and alcohol is associated with a 7.7-fold increased risk for traffic accidents.

Now, there is also emerging evidence that the use of benzodiazepines may increase the risk for developing dementia among older adults. This review evaluates the evidence from the literature on the association between benzodiazepine use and the risk for developing dementia.

Exploring the Literature and Evidence

A review of the literature indicates that there is a total of 15 studies that have evaluated the association between benzodiazepine use and the development of dementia. Four of the 15 studies were published prior to 2010 and 11 of the studies were published since 2010.

Although there are no randomized controlled trials (RCTs) looking at the association between benzodiazepine use and the risk for dementia, 6 prospective cohort studies, 6 case control studies, and 1 retrospective cohort study explore the relationship. Two studies had both a prospective cohort and a case control component. Three of the studies were conducted in France, 3 in Taiwan, 3 in Canada, 2 in the United Kingdom, and 1 each in Sweden, the United States, Switzerland, and Denmark.

Of the 15 studies, 8 showed a positive association between benzodiazepine use and the development of dementia, 6 prospective cohort studies, 4 were case control studies, and 1 was a retrospective cohort study. One positive study had a prospective cohort and a control arm to the study. The second meta-analysis that included data from 10 studies found the odds for developing dementia was higher by 78% among users those who were using benzodiazepines when compared to those who were not (OR=1.78). In the first meta-analysis, which included data from 6 studies, the investigators found the pooled adjusted risk ratios (aRRs) for the development of dementia was 1.49 for those who have used benzodiazepines, 1.55 for those who recently used benzodiazepines, and 1.55 for those who have previously used benzodiazepines, when compared with never users of benzodiazepines. The researchers stated the risk for dementia increased by 22% for every additional 20 defined daily doses of the drug per year (aRR=1.22).

The third meta-analysis that included data from 10 studies found the odds for developing dementia was higher by 78% among users those who were using benzodiazepines when compared to those who were not (OR=1.78). The investigators found a higher association when the studies were from Asia (OR=2.40), and a moderate association when the studies were from North America and Europe (OR=1.49).

The third meta-analysis that included data from 12 prospective and retrospective cohort studies and case-control studies found that benzodiazepines can be a risk factor for the development of dementia (OR=1.38).
### Table. Studies Showing Positive Association Between Benzodiazepine Use and the Risk of Dementia

<table>
<thead>
<tr>
<th>Study details (author, year, study type)</th>
<th>Assessment of cognitive impairment/dementia</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lagnaoui et al (2002)13</td>
<td>Neuropsychological tests (no detail given)</td>
<td>Ever use of benzodiazepines was associated with an increased risk of dementia (aOR=1.7).</td>
</tr>
<tr>
<td></td>
<td>DSM-III-R diagnosis of dementia</td>
<td>Former use was associated with an increased risk of dementia (aOR=2.3).</td>
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<td>made by a neurologist using all available information</td>
<td>No association was found between dementia and the current use of benzodiazepines (aOR=1.0).</td>
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<td>Clinical Modifications (ICD-9-CM) criteria for dementia</td>
<td>Cumulative dose (number of defined daily doses [DDD]):</td>
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<td>90 DDD ≤ cumulative dose &lt;180 DDD (aOR=1.28)</td>
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<td>≥180 DDD (aOR=1.39)</td>
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<td>Cumulative days:</td>
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<td>90 days ≤ using period &lt;180 days (aOR=1.38)</td>
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<td>Using period ≥180 days (aOR = 1.45)</td>
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<td></td>
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<td>Chronic use (&gt;6 months) (aOR=1.34)</td>
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<td></td>
<td>Clinical Modifications (ICD-9-CM) criteria for dementia</td>
<td>Compared to nonusers:</td>
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<tr>
<td></td>
<td></td>
<td>Current users (aOR= 2.71)</td>
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<td></td>
<td></td>
<td>Former users &lt;1 month (aOR= 2.40)</td>
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<td>1–3 months (aOR= 1.93)</td>
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<td>3–6 months (aOR= 1.49)</td>
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<td>6–12 months (aOR= 1.43)</td>
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<td></td>
<td>&gt;3 years (aOR= 1.08)</td>
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<tr>
<td>Gallacher et al (2011)11</td>
<td>DSM-IV criteria for non-vascular dementia</td>
<td>Compared to nonusers:</td>
</tr>
<tr>
<td></td>
<td>NINCDS-AIREN criteria</td>
<td>Dementia (OR=2.94, P=0.02)</td>
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<tr>
<td></td>
<td>Hachinski’s scale for vascular dementia</td>
<td>Vascular dementia (OR=3.61, P=0.07)</td>
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<td>Nonvascular dementia (OR=3.59, P=0.04) &lt;4 years</td>
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<td>Dementia (OR=3.48, P=0.03)</td>
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<td>Vascular dementia (OR=2.96, P=0.39)</td>
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<td>Nonvascular dementia (OR=6.61, P=0.02) &gt;4 years</td>
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<td>Dementia (OR=2.31, P=0.15)</td>
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<td>Vascular dementia (OR=3.38, P=0.08)</td>
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<td>Nonvascular dementia (OR=1.86, P=0.50)</td>
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<td>Clinical Modifications (ICD-9-CM) criteria for dementia</td>
<td>Compared to nonusers of hypnotics:</td>
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<td>Hazard Ratio (HR)=2.34 P&lt;0.001</td>
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<td>Men (HR=2.28, P&lt;0.001)</td>
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<td>Women (HR=2.39, P&lt;0.001)</td>
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<td>Age, 50-65 years (HR=5.22, P&lt;0.001)</td>
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<td>Age, &gt;65 years (HR=2.33, P&lt;0.001)</td>
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<td>Benzodiazepines (HR=2.56)</td>
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<td></td>
<td></td>
<td>Benzodiazepines versus non-benzodiazepines (HR=1.01)</td>
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<tr>
<td>Gage et al (2012)19</td>
<td>DSM-III-R diagnosis of dementia</td>
<td>Compared to nonusers:</td>
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<tr>
<td></td>
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<td>New use of benzodiazepines (aHR=1.60)</td>
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<td>After adjustment for depressive symptoms, new users of benzodiazepine (a HR=1.82)</td>
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<td>Nested case-control analysis</td>
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<td>Compared to nonusers</td>
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<td>Benzodiazepine ever user, (aOR=1.55)</td>
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<td>Recent users (aOR=1.48)</td>
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<tr>
<td></td>
<td></td>
<td>Past users (aOR=1.56)</td>
</tr>
<tr>
<td>Billioti de Gage et al (2014)20</td>
<td>Alzheimer disease (ICD-9)</td>
<td>Compared to nonusers:</td>
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<tr>
<td></td>
<td></td>
<td>Benzodiazepine ever users (aOR=1.43-1.51)</td>
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<td>1-90 daily doses (aOR=1.05-1.09)</td>
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<td>91-180 daily doses (aOR=1.28-1.32)</td>
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<td>&gt;180 daily doses (aOR=1.74-1.84)</td>
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<td>Short 11/2 (&lt;20 hours) (aOR=1.37-1.43)</td>
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<td>Long 11/2 (&gt;20 hours) (aOR=1.59-1.70)</td>
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<tr>
<td>Shash et al (2016)22</td>
<td>DSM-IV criteria</td>
<td>Compared to nonusers:</td>
</tr>
<tr>
<td></td>
<td>National Institute of Neurological and Communication Disorders and Stroke (NINCDS) criteria</td>
<td>Benzodiazepine users (adjusted HR (aHR)=1.10-1.14)</td>
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<tr>
<td></td>
<td>Alzheimer Disease and Related Disorders Association criteria</td>
<td>Long 11/2 (&gt;20 hours) (aHR=1.62-1.68)</td>
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<td></td>
<td>Short 11/2 (&lt;20 hours) (aHR=1.05-1.09)</td>
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The investigators concluded that the current evidence lacks the power to differentiate between the risks for the development of AD versus vascular dementias (VD), the risks when using long-acting versus short-acting benzodiazepines, and the risks based on the duration and the doses of the drugs that are used.

“[Salzman] advised that we must assume that the appropriate use of benzodiazepines will not lead to the development of AD.”

In his recent editorial in the American Journal of Psychiatry, Carl Salzman, MD, provided a counterpart to the question on whether benzodiazepines cause AD.18 Salzman stated that “there is little doubt that benzodiazepines like other sedative hypnotics may be associated with impaired cognition which is usually mild and dose-dependent.” He reported that the usual recommendations include only short half-life benzodiazepines at low doses and, if clinically possible, for brief periods of time. Salzman opined that future studies are needed regarding benzodiazepines and other medications’ possible associations with the development of late-life cognitive disorders. Until then, he advised that we must assume that the appropriate use of benzodiazepines will not lead to the development of AD. One caution with this editorial is that it cites a limited number of studies evaluating the association benzodiazepines and AD, and it is difficult to develop any definitive conclusions based on these studies.

The available evidence for the association between benzodiazepine use and the development of dementia should be evaluated based on the heterogeneity between the studies and limitations of each of these studies. These studies were conducted in different countries and had differing methodologies. In addition, many studies did not control for confounding variables including educational attainment, the presence of depression, anxiety, insomnia, and alcohol use. Also, 4 studies used the older DSM III-R criteria for the diagnosis of the dementia, causing concerns regarding the validity of the diagnosis. It is unclear whether the observed association between the use of benzodiazepines and the development of dementia is a causal effect, or the result of unmeasured confounding variables, as none of these studies were RCTs. Protopathic bias occurs when a pharmaceutical agent has been inadvertently prescribed for an early manifestation of a disease that has not yet been diagnosed. A prolonged lag phase between the first appearance of brain pathology associated with dementias, the development of clinical symptoms that may be risk factors for dementias including anxiety and depression, and the actual clinical diagnosis of dementia has led to investigators citing protopathic bias or “reverse causality” as the main area of controversy regarding the association between benzodiazepine use and the development of dementia.29 To prove a definitive association between benzodiazepine use and the development of dementia, the studies would have to be approximately 3 decades long given the prolonged course of neurodegenerative disorders like dementias.

There are 3 possible mechanisms that have been postulated for the association between benzodiazepine use and the development of dementia. For one, benzodiazepines possibly decrease activity of γ-aminobutyric acid (GABA), thereby promoting β-amyloid accumulation in the brain. Second, astrocyes near the β-amyloid accumulation in the brain secreting γ-aminobutyric acid (GABA), thereby promoting the negative cognitive effects of benzodiazepines. Finally, benzodiazepines may reduce the cognitive reserves by lowering brain activation levels.

Concluding Thoughts

Available evidence indicates a positive association between the use of benzodiazepines and the development of dementia, although causality cannot be inferred from this data. Despite the lack of evidence proving causality, the association between benzodiazepine use and the development of dementia is a major cause for concern given the prevalence benzodiazepine use among older adults. The prescription of benzodiazepines to older adults must be carefully reviewed given the lack of data regarding their long-term efficacy and their significant adverse effects including the risk for developing dementia.

Dr Tampi is the chairman of the department of psychiatry and behavioral sciences, Cleveland Clinic Akron General, Akron, OH. Dr Bennett is a psychologist in the Department of Psychiatry and Behavioral Sciences, Cleveland Clinic Akron General, Akron, OH.

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

REFERENCES


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SELECTED SAFETY INFORMATION

CONTRAINDICATIONS
- DAYVIGO is contraindicated in patients with narcolepsy.

WARNINGS AND PRECAUTIONS
- Central Nervous System (CNS) Depressant Effects and Daytime Impairment:
  DAYVIGO can impair daytime wakefulness. CNS depressant effects may persist in some patients up to several days after discontinuing DAYVIGO. Prescribers should advise patients about the potential for next-day somnolence.
  Driving ability was impaired in some subjects taking DAYVIGO 10 mg. Risk of daytime impairment is increased if DAYVIGO is taken with less than a full night of sleep remaining or at a higher than recommended dose. If taken in these circumstances, patients should not drive or engage in activities requiring mental alertness.
  Use with other classes of CNS depressants (e.g., benzodiazepines, opioids, tricyclic antidepressants, alcohol) increases the risk of CNS depression, which can cause daytime impairment. Dosage adjustments of DAYVIGO and concomitant CNS depressants may be necessary when administered together. Use of DAYVIGO with other insomnia drugs is not recommended. Patients should be advised not to consume alcohol in combination with DAYVIGO.
  Because DAYVIGO can cause drowsiness, patients, particularly the elderly, are at a higher risk of falls.

Please see additional Selected Safety Information on the following page and adjacent Brief Summary of DAYVIGO full Prescribing Information.

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SELECTED SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (CONT’D)

• Sleep Paralysis, Hypnagogic/Hypnopompic Hallucinations, and Cataplexy-Like Symptoms:
  Sleep paralysis, an inability to move or speak for up to several minutes during sleep-wake transitions, hypnagogic/hypnopompic hallucinations, including vivid and disturbing perceptions can occur with DAYVIGO. Prescribers should explain these events to patients. Symptoms similar to mild cataplexy can occur with DAYVIGO and can include periods of leg weakness lasting from seconds to a few minutes, can occur either at night or during the day, and may not be associated with identified triggering event (e.g., laughter or surprise).

• Complex Sleep Behaviors:
  Complex sleep behaviors, including sleep-walking, sleep-driving, and engaging in other activities while not fully awake (e.g., preparing and eating food, making phone calls, having sex), have been reported to occur with the use of hypnotics such as DAYVIGO. Events can occur in hypnotic-naïve and hypnotic-experienced persons. Patients usually do not remember these events. Complex sleep behaviors may occur following the first or any subsequent use of DAYVIGO, with or without the concomitant use of alcohol and other CNS depressants. Discontinue DAYVIGO immediately if a patient experiences a complex sleep behavior.

• Patients with Compromised Respiratory Function:
  The effect of DAYVIGO on respiratory function should be considered for patients with compromised respiratory function. DAYVIGO has not been studied in patients with moderate to severe obstructive sleep apnea (OSA) or chronic obstructive pulmonary disease (COPD).

• Worsening of Depression/Suicidal Ideation:
  Incidence of suicidal ideation or suicidal behavior, as assessed by questionnaire, was higher in patients receiving DAYVIGO than placebo (0.3% for DAYVIGO 10 mg, 0.4% for DAYVIGO 5 mg, and 0.2% for placebo). In primarily depressed patients treated with hypnotics, worsening of depression and suicidal thoughts and actions (including completed suicides) have been reported. Suicidal tendencies may be present in such patients and protective measures may be required. Intentional overdose is more common in this group of patients; therefore, the lowest number of tablets that is feasible should be prescribed at any one time. The emergence of any new behavioral sign or symptom of concern requires careful and immediate evaluation.

• Need to Evaluate for Comorbid Diagnoses:
  Treatment of insomnia should be initiated only after careful evaluation of the patient. Re-evaluate for comorbid conditions if insomnia persists or worsens after 7 to 10 days of treatment. Worsening of insomnia or the emergence of new cognitive or behavioral abnormalities may be the result of an unrecognized underlying psychiatric or medical disorder and can emerge during the course of treatment with sleep-promoting drugs such as DAYVIGO.

ADVERSE REACTIONS

• The most common adverse reaction (reported in 5% of patients treated with DAYVIGO and at least twice the rate of placebo) with DAYVIGO was somnolence (10% for DAYVIGO 10 mg, 7% for DAYVIGO 5 mg, 1% for placebo).

DRUG INTERACTIONS

• CYP3A Inhibitors: The maximum recommended dose of DAYVIGO is 5 mg no more than once per night when co-administered with weak CYP3A inhibitors. Avoid concomitant use of DAYVIGO with strong or moderate CYP3A inhibitors.

• CYP3A Inducers: Avoid concomitant use of DAYVIGO with moderate or strong CYP3A inducers.

USE IN SPECIFIC POPULATIONS

• Pregnancy and Lactation: There is a pregnancy exposure registry that monitors pregnancy outcomes in women who are exposed to DAYVIGO during pregnancy. Healthcare providers are encouraged to register patients in the DAYVIGO pregnancy registry by calling 1-888-274-2378. There are no available data on DAYVIGO use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. There are no data on the presence of lemborexant in human milk, the effects on the breastfed infant, or the effects on milk production. Infants exposed to DAYVIGO through breastmilk should be monitored for excess sedation.

• Geriatric Use: Exercise caution when using doses higher than 5 mg in patients ≥65 years old.

• Renal Impairment: Patients with severe renal impairment may experience an increased risk of somnolence.

• Hepatic Impairment: The maximum recommended dose of DAYVIGO is 5 mg in patients with moderate hepatic impairment. DAYVIGO is not recommended in patients with severe hepatic impairment. Patients with mild hepatic impairment may experience an increased risk of somnolence.

DRUG ABUSE AND DEPENDENCE

• DAYVIGO is a Schedule IV-controlled substance.

• Because individuals with a history of abuse or addiction to alcohol or other drugs may be at increased risk for abuse and addiction to DAYVIGO, follow such patients carefully.

Please see adjacent Brief Summary of DAYVIGO full Prescribing Information.

Reference: 1. DAYVIGO (lemborexant) [Prescribing Information]. Woodcliff Lake, NJ: Eisai Inc.
DAVIGO® (lmborexant) tablets, for oral use, CIV
Initial U.S. Approval: 2019
BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION 04/2020.

INDICATIONS AND USAGE
DAVIGO is indicated for the treatment of adult patients with insomnia, characterized by difficulties with sleep onset and/or sleep maintenance.

DOSE AND ADMINISTRATION
Dosing Information The recommended dosage of DAVIGO is 5 mg taken no more than once per night, immediately before going to bed, at least 7 hours remaining before the planned time of awakening; the dose may be increased to the maximum recommended dose of 10 mg based on clinical response and tolerability. Time to sleep onset may be delayed if taken with or soon after a meal.

Dosage Recommendations for Concomitant Use with CYP3A4 Inhibitors or CYP3A4 Inducers Co-administration with Strong or Moderate CYP3A4 Inhibitors: Avoid concomitant use of DAVIGO with strong or moderate CYP3A4 inhibitors. Co-administration with Weak CYP3A4 Inhibitors: The maximum recommended dosage of DAVIGO is 5 mg no more than once per night when co-administered with weak CYP3A4 inhibitors. Co-administration with Strong or Moderate CYP3A4 Inducers: Avoid concomitant use of DAVIGO with strong or moderate CYP3A4 inducers. Dosage Recommendations for Patients with Hepatic Impairment The maximum recommended dose of DAVIGO is 5 mg no more than once per night for patients with moderate hepatic impairment. DAVIGO is not recommended in patients with severe hepatic impairment.

CONTRAINDICATIONS
DAVIGO is contraindicated in patients with nasociliary.

WARNINGS AND PRECAUTIONS
CNS Depressant Effects and Daytime Impairment DAVIGO is a central nervous system (CNS) depressant that can impair wakefulness, including during nighttime, while driving, and may impair ability to remember events that occurred during the period of use. DAVIGO may cause or increase the effects of other CNS depressant medications, including alcohol, opioid analgesics, and other CNS depressant medications. DAVIGO may impair the ability to remember events that occurred during the period of use. DAVIGO may cause or increase the effects of other CNS depressant medications, including alcohol, opioid analgesics, and other CNS depressant medications. DAVIGO may impair the ability to remember events that occurred during the period of use.

Other Adverse Reactions Observed During Clinical Trials (Tables 1 and 2). Other adverse reactions of <2% incidence but greater than placebo are shown below. The following list does not include adverse reactions 1) for which a drug cause was remote, 2) that were so general as to be uninformative, or 3) that were not considered to have clinically significant implications.

DRUG INTERACTIONS
Drugs Having Clinically Important Interactions with DAVIGO

Table 1: Adverse Reactions Reported in ≥2% of DAVIGO-Treated Patients and at a Greater Frequency Than Placebo-Treated Patients During the First 30 Days of Study 1 and Study 2

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>DAVIGO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=422</td>
<td>5 mg n=422</td>
</tr>
<tr>
<td>Somnolence or fatigue*</td>
<td>1.3</td>
<td>6.9</td>
</tr>
<tr>
<td>Headache</td>
<td>3.4</td>
<td>5.0</td>
</tr>
<tr>
<td>Nightmares or abnormal dreams</td>
<td>0.9</td>
<td>2.9</td>
</tr>
</tbody>
</table>

*Combines preferred terms somnolence, lethargy, fatigue, sluggishness.

DRUG INTERACTIONS

Effect of Other Drugs on DAVIGO

- Strong, Moderate, and Weak CYP3A4 Inhibitors
  - Clinical Impact: Concurrent use with a strong, moderate, or weak CYP3A4 inhibitor may increase the risk of DAVIGO adverse reactions.
  - Interaction: Avoid concomitant use of DAVIGO with strong or moderate CYP3A4 inhibitors.
  - Examples: Strong CYP3A4 inhibitors: ketoconazole, clarithromycin, and eravacycline. Weak CYP3A4 inhibitors: co-trimoxazole, citalopram

- Strong and Moderate CYP3A4 Inducers
  - Clinical Impact: Concurrent use with a strong or moderate CYP3A4 inducer decreases lmborexant exposure, which may reduce DAVIGO efficacy.
  - Interaction: Avoid concomitant use of DAVIGO with strong or moderate CYP3A4 inducers.

- Alcohol
  - Clinical Impact: Concurrent use of alcohol increases lmborexant Cmax and AUC. Co-administration of DAVIGO with alcohol presents a numerically greater negative impact on postural stability and memory, as combined with alcohol intake when assessed near the Cmax of DAVIGO (2 hours post-dose).
  - Interaction: Avoid alcohol consumption with DAVIGO.
Table 2: Clinically Important Drug Interactions with DAVYGO (cont'd)

<table>
<thead>
<tr>
<th>Effect of DAVYGO on Other Drugs</th>
<th>CYP2B6 Substrates</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Import</strong></td>
<td></td>
</tr>
<tr>
<td>Concentration loss of DAVYGO increases the AUC of drugs that are CYP2B6 substrates, which may result in reduced efficacy for these concomitant medications.</td>
<td></td>
</tr>
<tr>
<td><strong>Interaction</strong></td>
<td></td>
</tr>
<tr>
<td>Patients receiving DAVYGO and CYP2B6 substrates concomitantly should be monitored for adverse clinical responses. Dose adjustments of CYP2B6 substrates may be considered on need.</td>
<td></td>
</tr>
<tr>
<td><strong>Examples</strong></td>
<td></td>
</tr>
<tr>
<td>Bipropamide, metoprolol</td>
<td></td>
</tr>
</tbody>
</table>

**USE IN SPECIFIC POPULATIONS**

Pregnancy: Pregnancy Exposure Registry: There is a pregnancy exposure registry that monitors pregnancy outcomes in women who are exposed to DAVYGO during pregnancy. Healthcare providers are encouraged to register patients in the DAVYGO pregnancy registry by calling 1-888-227-2276.

**Risk Summary**

There are no available data on DAVYGO use in pregnant women to evaluate for drug-associated risks of major birth defects, miscarriage or adverse maternal or fetal outcomes. In animal reproduction studies, oral administration of lebemoxar to pregnant rats and rabbits during the period of organogenesis caused toxicities only at high multiples of the human exposure at the highest recommended human dose (MRHD) based on AUC. The no observed adverse effect levels (NOAEL) are approximately 20 and 23 times the MRHD based on AUC in rats and rabbits, respectively. Similarly, oral administration of lebemoxar to pregnant and lactating rats caused toxicities only at high multiples of the human exposure at the MRHD based on AUC. The NOAEL is 95 times the MRHD based on AUC. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnant women have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2% to 4% and 15% to 20%, respectively. Data on lebemoxar’s administered orally to pregnant rats during the period of organogenesis is limited at dosages of 15, 73, 200, and 600 mg/kg/day, which are approximately 6 to >3000 times the MRHD based on AUC, lebemoxar caused maternal toxicity, manifested by decreased body weight and food consumption, decreased mean body weight, an increased number of dead fetuses, and skeletal, extralacral and visceral malformations (amphalecally, cleft palate, and membraneous ventricular septal defect) at >300 times the MRHD based on AUC. The NOAEL of 20 mg/kg/day is approximately 143 times the MRHD based on AUC. A 10% reduction in maternal body weight was observed at 100 mg/kg/day, and the NOAEL of 30 mg/kg/day is approximately 23 times the MRHD based on AUC. Lebemoxar caused maternal toxicity that consisted of decreased body weight and food consumption and a higher incidence of skeletal variations (presence of cervical ribs and supernumerary lumbar) at ≥200 mg/kg/day. The NOAEL of 30 mg/kg/day is approximately 23 times the MRHD based on AUC. Lebemoxar was administered orally to pregnant rats during pregnancy and lactation at doses of 35, 100, and 300 mg/kg/day, which are approximately 15 to 25× the MRHD based on AUC, lebemoxar caused maternal toxicity that consisted of decreased body weight, food consumption and toxicity to offspring consisting of decreased pup body weights, decreased femur length, and decreased ascitic fluid/stomach responses at 200× the MRHD based on AUC. The NOAEL of 200 mg/kg/day is approximately 93× the MRHD based on AUC, Lactation Risk Summary: There are data on the presence of lebemoxar in human milk, the effects on the breastfed infant, or the effects of breast milk production. Lebemoxar and its metabolites have been tested in the milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Infants exposed to DAVYGO through breast milk should be monitored for excessive sedation. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for DAVYGO and any potential adverse effects on the breastfed infant from DAVYGO or from the underlying maternal condition. Pediatric Use: The safety and effectiveness of DAVYGO have not been established in pediatric patients. Geriatric Use: The total number of patients treated with DAVYGO (n=148) in controlled studies (n=148) was of patients 65 years old. In one subgroup of studies (the elderly subgroup), 76 (55%) were 65 years of age or older. The incidence of adverse events was similar in patients 65 years old and younger and those 75 years of age or older. Overall, efficacy results for patients ≥65 years of age were similar to patients <65 years old. In a pooled analysis of Studies 1 and 2 (the first 30 days) and Studies 2, the incidence of somnolence in patients ≥65 years old with DAVYGO 10 mg was higher (9.8%) compared to 7.3% in patients ≤65 years old. The incidence of somnolence with DAVYGO 5 mg was similar in patients ≥65 years old (4.9%) and <65 years old (5.1%). The incidence of somnolence in patients treated with placebo was 2% or less regardless of age. Because DAVYGO can increase somnolence and drowsiness, patients, particularly the elderly, are at a higher risk of falls. Exercise caution when using doses >5 mg in patients ≥65 years old. Renal Impairment: No dose adjustment is required in patients with mild, moderate, or severe renal impairment. DAVYGO exposure (AUC) was increased in patients with severe renal impairment. Patients with severe renal impairment may experience an increased risk of somnolence. Hepatic Impairment: DAVYGO has not been studied in patients with severe hepatic impairment, and in this population, the recommended DAVYGO exposure (AUC) and terminal half-life were increased in patients with moderate hepatic impairment. (Child-Pugh class B). Dose adjustment is recommended in patients with severe hepatic impairment (Child-Pugh class C). DAVYGO exposure (AUC) was increased in patients with moderate hepatic impairment (Child-Pugh class B), but the terminal half-life was not changed. Patients with mild hepatic impairment may experience an increased risk of somnolence. Patients with Compromised Respiratory Function: In a study of patients with mild ASA (American Society of Anesthesiologists) class I (15 events per hour of sleep), DAVYGO did not increase the frequency of obstructive events or cause oxygen desaturation. DAVYGO has been evaluated in patients with COPD or moderate to severe OSA. Clinically meaningful respiratory effects of DAVYGO in COPD or moderate to severe OSA cannot be excluded.

**DRUG USE AND DEPENDENCE**

Controlled Substance: DAVYGO contains lebemoxar, a Schedule IV controlled substance. Abuse is intentional, nontherapeutic use of a drug, even once, for its desirable physical or psychological effects. In a human abuse potential study conducted in recreational substance users (n=20), lebemoxar at 10 mg, 36 mg, 30 mg and 30 times the maximum recommended dose, produced responses on positive subjective measures such as “Drug liking,” “Overall Drug liking,” “Like Drug Again,” and “Good Drug Effects” that were statistically similar to those produced by the sedatives zolpidem (30 mg) and suvorexant (40 mg), and statistically greater than the responses on these measures that were produced by placebo. Because individuals with a history of abuse or addiction to alcohol or other drugs may have an increased risk for abuse and addiction to DAVYGO, follow such patients carefully. Dependence: Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug. Animal studies and clinical trials evaluating physical dependence chronic administration of lebemoxar did not produce withdrawal signs or symptoms upon drug discontinuation, this suggests that lebemoxar does not produce physical dependence.

**OVERDOSE**

There is limited clinical experience with DAVYGO overdose. In clinical pharmacology studies, healthy patients who were administered multiple doses of up to 75 mg (15 times the maximum recommended dose) of DAVYGO showed dose-dependent increases in the frequency of somnolence. There is no available specific antidote to an overdose of DAVYGO. In the event of overdose, standard medical practices for the management of any overdose should be used. In managing overdose, provide supportive care, including close medical supervision and monitoring and consider the possibility of multiple drug involvement. Consult a Certified Poison Control Center or refer to the toxicologic information on the management of overdosage at 1-800-222-1222 or www.poisontech.org. The value of dialysis in the treatment of overdose has not been determined with lebemoxar. An lebemoxar is highly protein-bound, hemodialysis is not expected to contribute to elimination of lebemoxar.

**CLINICAL STUDIES**

Special Safety Studies: Middle of the Night Safety: The effect of DAVYGO on middle of the night safety was evaluated in a randomized, placebo- and active-controlled trial in healthy female subjects ≥55 years or male subjects ≥65 years. Postural stability, the ability to awaken in response to a sound stimulus, and attention and memory were assessed following a scheduled awakening 6 hours after the start of the 8-hour time in bed. Postural stability was measured by assessing body sway using an ataxia meter. Nighttime dosing of DAVYGO 5 mg and 10 mg resulted in impairment of balance measured by body sway area at 6 hours as compared to placebo. The ability to awaken to sound in the middle of the night was assessed using an audiometer that delivered 1000 Hz tones at 100 dB. There were no meaningful differences between DAVYGO 5 mg (or 10 mg) and placebo on ability to awaken to sound. A comprehensive performance assessment battery was administered to assess attention and memory after middle of the night awakening 14 hours postdosed in subjects receiving DAVYGO 5 mg or 10 mg or placebo on middle of the night postural stability or memory compared to placebo. Effects on Sleep: A randomized, double-blind, placebo- and active-controlled, four-period crossover study evaluated the effects of nighttime administration of DAVYGO on next morning driving performance approximately 9 hours after dosing in 24 healthy elderly subjects (65 years, median age 67 years: 14 men, 10 women) and 24 adult subjects (median age 49 years: 12 men, 12 women). The primary driving performance outcome measure was change in Standard Deviation of Latitude, Position, (SDLP). Testing was conducted after one night (a single dose) and after eight consecutive nights of treatment with DAVYGO. Although DAVYGO at doses of 5 mg and 10 mg did not cause statistically significant impairment in next-morning driving performance in adult or elderly subjects (compared with placebo), driving ability was impaired in some subjects taking 10 mg DAVYGO. Patients using the 10 mg dose should be cautioned about the potential for next-morning driving impairment because there is individual variation in sensitivity to DAVYGO. Residual Insomnia: Residual insomnia was assessed by comparing sleep diary- recorded SDLP and SWAOSO from the screening period to the two weeks following treatment discontinuation in both Studies 1 and 2. Analyses of group means and the proportion of patients with residual insomnia suggest that DAVYGO was not associated with residual insomnia following treatment discontinuation. Withdrawal Effects: In 12-month and 1-month controlled safety and efficacy trials (Studies 1 and 2, respectively), withdrawal effects were assessed in the first 12 months of treatment. Withdrawal symptoms were captured following discontinuation from study drug in patients who received DAVYGO 5 mg or 10 mg. There was no evidence of withdrawal effects following discontinuation at either dose.

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Talking to Patients and Rediscovering Disordered Selfhood in Schizophrenia

Josef Parnas, MD, DrMed Sci, and Maja Zandersen, MSc, PhD

Disordered selfhood may be a core phenotypic trait of schizophrenia spectrum disorders. This article is written from a European phenomenological psychiatric perspective.1 In Anglophone psychiatry, phenomenology refers to a simple layman description of signs and symptoms, the latter preferably in their behavioral aspects. The symptom is viewed as a well-defined, quasi-objective entity liable to unproblematic quantification. For example, using the structured interview presupposes the conception of a symptom as a pre-existing ripe fruit only waiting for a push from a pre-formed question in order to come into full view.2

The term phenomenology used here is different from American usage. It refers to a faithful exploration, description, and conceptualization of the patient’s contents and structures of subjective life and modes of existence (eg, not only the content of the delusion but its mode of emergence and articulation and ways of experiencing the delusion).

Such an approach should minimally include:
1. Interviewing the patient in a way that maximizes their spontaneous self-descriptions, which can provide concrete and manifold examples of their abnormal experiences. This requires a non-judgmental attitude that prevents the clinician from prematurely reifying and classifying the patient’s inner life.
2. Such an interview, however, also requires that the clinician is knowledgeable, possessing a rich conceptual repertoire. An old dictum says, “perception without concept is blind.” In other words, if you are not well-read or trained, you will not be able to hear what the patient is trying to convey to you.

The rediscovery mentioned in the title concerns a profound dis-order of subjective life in schizophrenia. Distortions of subjective life for the patient is often their usual mode of existing in the world, and they only become accessible for the interviewer when they successfully facilitate the patient’s self-reflection and verbalization. The following patient perspective provides a clear idea what is at stake:

This dissolved self... It is a truly dissolved self. I feel that I am everywhere and nowhere at the same time. It is like a dream in which I am not present. It is like a sea where you can see fishes and plants and there is a current of water. It is in such a way that I feel that I am present. Not as a fish or a plant but as a current of water. My life feels like a manuscript written by someone else. I am open to the idea that my childhood was not my own. That my childhood is somebody else’s and that I have taken it over in some way. If you said to me that what I am telling you actually is about my friend instead of me, then I would be open to this suggestion. That my ideas stem from a movie or from another person.

This very metaphorical and evocative narrative conveys that the patient seems to lack a stable and substantial sense of self as an anchor and a vantage point. Normally our sense of self permeates our thinking, perceiving, and feeling. This patient experiences a disconnection from her thinking, speaking, and remembering, involving a global alienation toward herself. Although such rich descriptions are not very frequent, most of the patients are able to verbalize similar experiences in a more restricted vocabulary.

What is the Self?
Phenomenology distinguishes between the narrative self (personality) and the minimal or basic self.3 If you ask a random individual on the street “who are you?” the person may respond “I am Paul Brown, 30 years old, working as an engineer.” He may proceed with information about his life history, his characterological traits, cognitive abilities, preferences and goals, and the like. This level of selfhood we usually call personal identity or, in technical terms, the narrative self.

This level of selfhood is a complex and continuously evolving self and self-identity that is anchored in the individual’s biography and heavily dependent on language and memory. It is a narrative that contributes to create a self-coherence for ourselves and others. However, Paul Brown will certainly not tell us that he is experiencing everything in the first-person perspective; yet the first-person perspective is the condition for all these complex personality features to emerge.

This is the level of the so-called “minimal” or “basic” self, which implies that all my experiences (perceiving, thinking, remembering) articulate themselves as my experiences. When I am thinking about something, I do not ask myself who is doing the thinking. But this dimension of me (me-ness or mine-ness) is simply a tacit, automatic, and pre-reflective dimension of all my mental life. This elementary sense of selfhood also implies a sense of self-coincidence (I am always at one with myself) and affectively felt self-presence and self-persistence.

This basic self is the most intimate nucleus around which more complex features of the narrative self-coalesce. We believe that the central disorder of schizophrenia and schizotypal disorder consists in the instability of the basic self, leading to varieties of self-alienation, basic identity problems, and a whole area of cognitive and other disturbances.

Table. The 5 Domains of EASE

<table>
<thead>
<tr>
<th>Domains of EASE</th>
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</thead>
<tbody>
<tr>
<td>Alienations of cognition</td>
</tr>
<tr>
<td>Disorders of basic self</td>
</tr>
<tr>
<td>Disorders of embodiment</td>
</tr>
<tr>
<td>Disorders of ego-boundaries</td>
</tr>
<tr>
<td>Existential changes</td>
</tr>
</tbody>
</table>

Historical Background
By the end of the 1990s, we proposed that the fundamental phenotypic feature of the schizophrenia spectrum was an instability in the very basic experiential structures of consciousness (ie, self-disorders), an idea originally advanced by the scholars who founded the concept of schizophrenia (eg, Kraepelin, Bleuler, Schneider, Minkowski).4 Our hypothesis was based on empirical research in US-Denmark high-risk studies and genetic linkage studies and on clinical experience with patients with first-onset schizophrenia.4 During this research, we noticed that the patients with beginning schizophrenia consistently complained of alarming disturbances gravitating around their very sense of being a self (eg, describing an unstable sense of being a self-present, unified, and persistent subject). The patients complained of lacking a core, lacking a kind of substantiality that could function as an anchoring point for their perspective, feelings of being ephemeral, not really present either in themselves or in the world, and experiencing an increasing alienation in the form of a distance between their own sense of being a subject and their thoughts and perceptions.

They also complained about loss of meaning and of naturalness and obvi-ousness of the surrounding world and social relations, “other people seem to have some knowledge that I am completely lacking” (ie, in phenomenological terms, disorders of common sense).5 It is not a question of understanding complex cognitive tasks but simply of a lack of attunement and
Figure. Depiction of Psychopathological Phenomena in Schizophrenia at a Schizotypal and Psychotic Level

**Disorder of Basic Self**
- Diminished self-saturation of subjective life
- Feeling different (Anderssein)
- Problems with “common sense”

**Experiential Distance to Mental Content and the Body**
- Pressure of thoughts, interfering thoughts, thoughts aloud
- Diminished sense of presence
- Involuntary self-observation
- Anhedonia

**Frank Psychosis**
- Hallucinations, influence phenomena
- Primary delusion

Personality disorder, obsessive-compulsive disorder, and autistic spectrum disorders.

Self-disorders are unrelated to neurocognitive dysfunctions and correlate weakly or moderately with positive and negative symptoms. They exhibit a remarkable temporal stability over 5 to 7 years and predict development of psychosis in the ultra-high-risk population. A recent prospective study of adolescents who were help-seeking and nonpsychotic predicted a schizophrenia spectrum disorder (schizophrenia and schizotypal disorder) in early adulthood 7 years later (sensitivity of 78% and specificity of 67% at a cutoff score of 6 EASE-items).

It is important to realize that self-disorders as a trait feature are equally characteristic of schizotypal disorder and schizophrenic psychosis. There is also an emerging neuroscience literature on self-disorders.

The empirical research is consistent with the hypothesis that self-disorders constitute the core phenotype of schizophrenia. One could perhaps consider this statement as a banality or a tautology since the very original concept of schizophrenia was constitutively associated with the clinical evidence of self-disintegration. The Case Vignette illustrates case of the evolution of schizophrenia.

**Case Vignette**

"Olga" is a 31-year-old, single, never married woman. She works in a hospital laboratory as a biochemist. She has always been isolated and felt uncomfortable in the company of others. She has always been a loner, feeling different from others, and has always been fascinated by the idea of being a (delusional) idea of being substituted as an infant; moreover, it is a delusion that seems to involve some sort of psychological resolution. Thus, the sense of being different from others precedes finding out what is different.

In German psychiatry this phenomenon has been known as Anderssein. It refers to a sense of a fundamentally different existential position that the patient cannot easily conceptualize and verbalize, but uses vague but comprehensive phrases like “I felt wrong.” Experience of Anderssein is quite specific to schizophrenia spectrum disorders but is practically unknown in contemporary psychiatry.

Our patient seems to have disorders of common sense; she feels uncomfortable in the company of others and manifests a phenomenon of “involuntary self-witnessing” where she involuntarily observes herself during interaction with others. This differs from an introspective self-observation because the sense of subjectivity is doubled, so to say, and neither of the 2 consciousnesses functions as a self-observation.

It seems that the self-disorders of this patient play a generative role in her psychopathology. A schematic phenomenological proposal of symptom evolution is outlined in the Figure. In general terms, the disorder of basic self in schizophrenia leads to a self-alienation where fragments of the self become another that manifest as voices, external influences, or characteristic delusions.

**Implications and Conclusion**

Self-disorders research has important theoretical and therapeutic consequences. Schizophrenia spectrum is not seen as a contingent mixture and meaningless collection of positive and negative symptoms but as an expression of profound structural changes of subjective life that often cause suffering, other pathological phenomena, and varieties of dysfunctions.

A familiarity with self-disorders enables the clinician to understand certain meaningful patterns of psychopathology and re-humanizes the patient-clinician relationship. Furthermore, such familiarity improves differential diagnosis, especially in the early stages of the illness and opens up novel psychotherapeutic approaches. Finally, a pathogenetic focus on a core phenotype may be more useful and fruitful than the comes infused with delusional content. Our patient describes a sense of not belonging since early childhood. Later this becomes thematicized as a (delusional) idea of being substituted as an infant; moreover, it is a delusion that seems to involve some sort of psychological resolution. Thus, the sense of being different from others precedes finding out what is different.

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INDICATIONS AND USAGE
Drizalma Sprinkle™ (duloxetine delayed-release capsules) is a serotonin and norepinephrine reuptake inhibitor (SNRI) indicated for:
- Major Depressive Disorder (MDD) in adults
- Generalized Anxiety Disorder (GAD) in adults and pediatric patients aged 7 to 17 years old
- Diabetic Peripheral Neuropathic Pain (DPNP) in adults
- Chronic Musculoskeletal Pain in adults

CONTRAINDICATIONS
Serotonin Syndrome and MAOIs: Do not use MAOIs intended to treat psychiatric disorders with Drizalma Sprinkle™ or within 5 days of stopping treatment with Drizalma Sprinkle™. Do not use Drizalma Sprinkle™ within 14 days of stopping an MAOI intended to treat psychiatric disorders. In addition, do not start Drizalma Sprinkle™ within 14 days of stopping treatment with Drizalma Sprinkle™. Do not use MAOIs intended to treat psychiatric illness within 14 days of stopping treatment with Drizalma Sprinkle™.

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

GLUCOSE CONTROL IN DIABETES
In diabetic peripheral neuropathic pain patients, small increases in fasting blood glucose and HbA1c have been observed.

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

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

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

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study of causally distant symptoms such as delusions and hallucinations.

Dr Parnas is professor of psychiatry, Mental Health Centre Glostrup, Faculty of Health and Medical Sciences, University Hospital of Copenhagen; and Center for Subjectivity Research, Faculties of Humanities, University of Copenhagen, Denmark. Dr Zanderson is clinical psychologist and part-time lecturer, Mental Health Centre Glostrup, University Hospital of Copenhagen; and Faculties of Social Sciences, University of Copenhagen. They report no conflicts of interest concerning the subject matter of this article.

REFERENCES


Improving Care in Teens With Opioid Use Disorder

**Laurie Martin**

In the midst of a nationwide opioid epidemic, there is a population that is largely being ignored. According to a large cohort study, only a small percentage of teens receive proper aftercare following near-fatal overdoses. Alinsky and colleagues examined data from more than 4 million Medicaid enrollees (N=4,039,216) and found that only 1 in 54 youths aged 13 to 22 years received evidence-based pharmacotherapy after an overdose. Unfortunately, it appears that proper care in this patient population is given in very few cases (Table).

*Psychiatric Times* invited lead author Rachel H. Alinsky, MD, MPH, to share insights from the study. Alinsky is an adolescent medicine and addiction medicine fellow at Johns Hopkins University School of Medicine in Baltimore, Maryland.

**PT:** Your research highlights the need for quality treatment, especially for younger patients. What insights can you provide about interventions and obstacles to treatment?

**RACHEL H. ALINSKY, MD, MPH:** We need to find effective interventions that can link adolescents and young adults directly into treatment after an opioid overdose. We also need to evaluate the barriers to accessing care at the time of overdose (such as insurance restrictions, lack of community providers or treatment centers, and stigma), and find strategies to mitigate these barriers. System-level changes are necessary, such as targeting federal funding for research and treatment for youth, decreasing insurance barriers, and increasing the availability of youth-serving physicians and addiction treatment centers.

**PT:** In the study, you and your colleagues noted, “Nonfatal opioid overdose may be a critical touch point when youths who have never received a diagnosis of opioid use disorder can be engaged in treatment.” Is that because these youths have hit rock bottom?

**ALINSKY:** In the addiction treatment field, we do not abide by that old adage—that people have to hit rock bottom before they are ready to get treatment. That is somewhat of a myth. What we are trying to emphasize in our article is that overdose is a particularly crucial time when we can draw someone into treatment because they are presenting into the medical setting, seeing doctors, and we have this opportunity to interact with them and offer them treatment. Coming into the emergency department with an overdose may be the only time this person is sitting face-to-face with a doctor, and we want to capitalize on this opportunity to offer the best care we can to the patient.

Of course, that does not mean they did not want treatment a month ago or a week ago—they very well might have wanted treatment but did not know how to access it in our very difficult-to-navigate addiction treatment system. So when the patient is physically with us after an overdose, we have the chance to help them gain access to lifesaving treatment.

**PT:** What are the key takeaway points from the study?

**ALINSKY:** Prior to this study, we knew that teens and young adults were about one-tenth as likely as adults to receive treatment for opioid use disorder in general. And while we knew that more than 4000 adolescents and young adults between the ages of 15 and 24 die from an opioid overdose every year, very little was known about health care use following nonfatal opioid overdose in youth. We were interested in figuring out the extent to which adolescents and young adults are receiving evidence-based treatment after a nonfatal opioid overdose.

We found that fewer than 1 in 50 adolescents and young adults who had an opioid overdose received the standard-of-care medication treat-

---

### Table. Overdose Deaths in Young Adults Due to Opioids

<table>
<thead>
<tr>
<th></th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
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<td>1700</td>
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<td>2491</td>
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<td>1812</td>
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<td>641</td>
<td>833</td>
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<td>1058</td>
<td>1388</td>
<td>1536</td>
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<td>489</td>
<td>658</td>
<td>829</td>
<td>833</td>
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<tr>
<td><strong>Prescription Opioids AND Other Synthetic Narcotics</strong></td>
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<td>21</td>
<td>31</td>
<td>28</td>
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<td>52</td>
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<tr>
<td><strong>FEMALE</strong></td>
<td>10</td>
<td>12</td>
<td>23</td>
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<td><strong>MALE</strong></td>
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<td>12</td>
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<td>19</td>
<td>27</td>
<td>38</td>
<td>29</td>
<td>44</td>
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</table>

1. Any Opioid ICD-10 codes (T40.0-T40.4, T40.6)
2. Prescription Opioids ICD-10 codes (T40.2-T40.3)
ment that is recommended by the American Academy of Pediatrics.\(^1\) We also found that youths with opioid overdose have a high risk of recurrent overdose; more than 8% of youths with heroin overdose experience another overdose within 3 months.\(^1\)

When an adolescent or young adult goes to the hospital with an emergency, you expect them to get the treatment they need. But here we see that less than 2% are getting that treatment, which would not be acceptable for any other medical condition. In pediatrics, it would be unacceptable if only 1 in 50 youths with asthma [received] the standard treatment when they came into the emergency department, or if 1 in 50 youths with diabetes [received] the standard treatment when they were hospitalized with diabetic ketoacidosis. Pediatricians would not find that treatment gap acceptable. Yet this is where we are now with the treatment for youths who have an opioid overdose—and we need to do better for them.

Additionally, with such high rates of recurrent overdose, it is even more important to get these youths into effective treatment as soon as possible, so we can try to prevent another overdose.

Finally, prescribing practices should be closely monitored in young people; they are a critically neglected patient population when it comes to addiction monitoring. As verified in an earlier study of 2,752,612 adolescents: “Safe opioid prescribing practices are critical to mitigate the risk of prescription opioid overdose in adolescents and young adults.”\(^2\)

**PT:** What are the key issues in recognizing opioid use disorder in youth?

**ALINSKY:** The diagnosis of opioid use disorder is straightforward and is based on how many criteria an individual meets from a set of 11 criteria defined in DSM-5. In the case of youths who are presenting with opioid overdose, there is a chance that clinicians may view this as a standalone incident, and not recognize it as a manifestation of an adolescent’s underlying opioid use disorder. Thus, clinicians should be thinking about, and evaluating for, opioid use disorder in any youths that present with an overdose.

Clinicians should probe for issues such as taking the opioid in larger amounts than intended, unsuccessful efforts to cut down use, cravings, recurrent use despite failure to fulfill obligations at school or home, or current use in physically hazardous situations.

In terms of treatment, psychiatrists and other providers should offer medication for opioid use disorder as first-line treatment, consistent with recommendations from the American Academy of Pediatrics. These medications include buprenorphine, methadone, and naltrexone. Pharmacological interventions can be combined with behavioral health services such as therapy or counseling. The provider will need to determine the level of care that will best support the patient in their current stage of treatment—inpatient hospitalization, residential treatment, intensive outpatient, or outpatient treatment.

We know that medication is effective and lifesaving for opioid use disorder; large studies in adults have found that medication cuts the risk of death in half.\(^3\) We also know that youths who are on medication stay in treatment longer.\(^4\) Because so few youths actually ever receive this effective addiction treatment, an overdose can be an ideal opportunity to link someone into care who has not been able to access it previously.

**PT:** How can clinicians advise their patients and families on finding the most appropriate care?

**ALINSKY:** Patients and their parents can advocate for treatment by asking their doctors about treatment when they are in the emergency department with an overdose. Some emergency departments have programs where patients can immediately start on medication treatment; the programs can then link them to a provider in the community. These programs have been shown to be extremely effective, with much higher rates of individuals entering and staying in treatment than if someone is simply handed a phone number to call to set up treatment.” If that sort of linkage is not available, families should ask to be referred so their teen or young adult can receive treatment in their community as soon as possible.

Clinicians or patients and families who want to find available treatment resources within their community can use the treatment locator provided by the Substance Abuse and Mental Health Services Administration (https://findtreatment.samhsa.gov/). Here you can enter your zip code and find all the available addiction treatment centers, sorting by services offered. It is also possible to specifically look for buprenorphine prescribers or methadone programs from that web page.

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**REFERENCES**


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### All underlying causes of death* | Source: National Center on Health Statistics, CDC WONDER

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<thead>
<tr>
<th></th>
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*Includes deaths with underlying causes of unintentional drug poisoning (X40–X44), suicide drug poisoning (X60–X64), homicide drug poisoning (X85), or drug poisoning of undetermined intent (Y10–Y14), as coded in the International Classification of Diseases, 10th Revision. Years for which data are not provided include unreliable data. Blank fields designated by unreliable or suppressed data. For more information visit CDC WONDER.
COMMENTARY

My Patient Lost Their Job...Now What?

>> David “Daven” E. Morrison, MD, Andrew Brown, MD, Sean Sassano-Higgins, MD, QME, Ashley H. VanDercar, MD, JD, Barbara Long, MD, PhD, FABPM, and Fara R. White, MD

work is central to many people’s lives. The average person spends one-third of their adult life working, yet psychiatrists may neglect work when assessing a patient’s well-being. We address drug use, family life, and psychiatric symptoms, but may not fully appreciate how those factors are relevant to our patient’s work. Nonetheless, work is tied to the surge in mental health concerns precipitated by the coronavirus disease 2019 (COVID-19) pandemic. As we consider anxiety, depression, substance use, spousal and child abuse, and loneliness, all of which have been found to increase following disasters, we must not forget how the pandemic is affecting our workforce. For instance, during this time of increased social isolation, employers have been using video technology to maintain a sense of connectedness among their employees. This very much reflects the centrality of work to mental health and social cohesion. Psychiatrists will find it difficult to ignore the centrality of work over the coming months, as the pandemic has led to a surge in unemployment not seen since the Great Depression. Individuals filed more than 58 million initial unemployment benefit claims between March 14 and August 22.

Table. Components of a Work History

| What did their parents do for work? What did the patient think about their parents’ occupation? |
| What did the patient expect to do for work when they grew up? |
| How did the patient end up in their current job? |
| What was the patient’s motivation for accepting past jobs? |
| What were the patient’s expectations with past jobs? |
| Did past jobs live up to those expectations? |
| What led to past job transitions? |
| What are, or were, the daily tasks of the current or most recent job? |
| What skills/training/qualifications does the patient possess? |
| What are the current job market opportunities? |
| What interpersonal areas have they struggled with during past employment (eg, too aloof or too friendly)? |

2020, and economists anticipate more will follow. When a patient loses their job, a psychiatrist must respond actively and swiftly. Employment fulfills essential biological, psychological, and social needs. It is the means by which we sustain ourselves, comprises a large part of our identity and social community, and determines how we spend most of our waking hours. As such, job loss is profoundly disorienting, challenging the very meaning and purpose of life. It directly affects self-esteem and perceptions of self-worth, precipitates anxiety, and increases the chance of physical and mental illness. Unemployment is associated with lower motivation, and an increased risk of substance abuse and suicide. This is compounded by the loss of structure and shared experience that work typically confers. Thus, job loss generally leads to a loss of well-being.

When a patient loses their job, the psychiatrist has 4 tasks: (1) triage and treat imminent emergencies; (2) treat acute or latent psychiatric symptoms medically or psychotherapeutically; (3) support the patient by helping them to recognize vulnerability, identify feelings, and enhance personal support systems; and (4) prompt the patient to realistically evaluate their future job prospects. Treating emergencies and psychiatric disorders, as well as discussing the effects of job loss on personal and interpersonal variables can lead to improvement. Clinicians can do this informally or psychotherapeutically. Helping the patient identify their social support systems and how to use them can be helpful. As with any episode of clinically significant depression, anxiety, or psychosis, medication may be indicated.

Returning to work is the ultimate goal for the majority of our patients. To evaluate job prospects realistically, psychiatrists should take a work history once the initial crisis and reactions have been explored. Assessing a work history is not typically taught during residency training and is often not part of a clinical interview. However, a work history provides important information about a patient’s functionality (Table). Work history questions help patients identify what they wish to do for future employment, including a change in career. Expectations, skills, and qualifications can be realistically assessed by discussing patient responses. The psychiatrist can serve as a sounding board for the patient’s ideas and help the patient cultivate adaptive perceptions, expectations, and realistic future plans.

How do psychiatrists carry out this function? Perhaps the most important principle to consider is their role in serving as a source of reality testing and as a means of integrating the self. By listening to the patient’s occupational hopes and integrating these with the current reality and the work history, the psychiatrist can explore what is possible in a career. The psychiatrist and the patient may uncover a wider range options for work than the patient would discover in isolation.

It is clear that the pandemic will continue to affect the economy, the job market, and work. It is likely that many aspects of work—such as where, how, and for whom it is conducted—will change, and many changes will persist beyond the pandemic. We may wish to recall that our society, economy, and work situations were far from perfect prior to the pandemic; perhaps the crisis can be reframed as an opportunity for our patients to seek healthier and more meaningful work situations.

Job loss is likely to affect far more people than COVID-19 itself. Psychiatrists are uniquely positioned to sustain the unemployed individual’s sense of efficacy, identity, and purpose during these difficult times. By understanding and supporting our patients, we can help them avoid the downward spiral of helplessness and despair that can otherwise follow job loss.

Dr Morrison is an assistant clinical professor of psychiatry at Chicago Medical School in Illinois. Dr Brown is a department psychiatrist at Boston Police Department in Massachusetts. Dr Sassano-Higgins is an adjunct professor of psychiatry at the University of Southern California, and chair of the Committee on Work & Organizations for the Group for the Advancement of Psychiatry. Dr VanDercar is a forensic psychiatry fellow at the University Hospitals Cleveland Medical Center and Case Western Reserve University School of Medicine in Ohio. Dr Long is the president-elect for the Group for the Advancement of Psychiatry. Dr White is an adjunct voluntary faculty member at Northwell Health System in New York City, New York.

REFERENCES


The Psychiatric Potential of Statins

Seetal Dodd, PhD, Anna Giménez Palomo, MD, and Michael Berk, PhD, MBCHB, MMED, FFPsychSA, FRANZCP

Decades of research have investigated inflammation and mental illness, suggesting that there is a robust and complex link. However, the link lacks diagnostic specificity and varies considerably among individuals, and with each stage of illness. Chronic, low-grade inflammation appears to precede the initial illness episode, at least in some individuals. Drugs that modulate the immune system may also affect an individual’s mood and have possible psychiatric adverse effects (AEs). Perhaps the best example is that interferon-α treatment of hepatitis C precipitates depressive episodes. Successful antidepressant treatment is associated with reduction in inflammatory markers.

Statins are best known as competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. Statin treatment results in lower low-density lipoprotein cholesterol levels and in benefits to cardiovascular health. Statins also have anti-inflammatory mechanisms of action, including T-cell downregulation, suppression of cytokines, production of chemokines and C-reactive protein, and downregulation of transcription factors. In a post hoc, pooled analysis (N = 1,969) of data collected at baseline and at a 1-year follow-up from a study of patients with acute coronary syndrome, statin treatment was shown to reduce levels of interleukin (IL)-6 and IL-18. Raised levels of these cytokines appeared to predict depression after acute coronary syndrome.

Addressing Depression Symptoms

Many epidemiological studies have shown that treatment with statins is associated with a lower risk for depression (Table 1). A population cohort study (N = 4,407,990) using Swedish national registry data investigated the relationship between statin use and the development of depression. The use of any statin was associated with an 8% decrease in risk for depression (odds ratio [OR], 0.92) compared with individuals who did not use statins. Elsewhere, in a cohort of individuals 55 years and older (N = 2,804), statin use was associated with decreased depression (OR, 0.71). However, no association between statin use and depression was determined in an analysis of data from 19,114 individuals, most of whom were 70 years and older, of whom 5987 used statins.

Evidence from clinical trials suggests that, adjuvant to treatment with antidepressants, some statins are associated with better treatment outcomes. A recent meta-analysis showed that treatment with lovastatin, atorvastatin, and simvastatin, adjunctive to antidepressant treatment, was superior to treatment with a placebo adjunctive to antidepressant treatment for improving depression (indexed by the Hamilton Depression Rating Scale). More recently, the results of a trial of rosuvastatin for young individuals with depression indicated that rosuvastatin failed to beat the placebo on the primary outcome, but it was positive on a number of secondary outcome measures, leaving the benefit uncertain.

The Use of Statins in Schizophrenia

A trial comparing simvastatin (n = 33) with placebo (n = 33) in participants with schizophrenia treated with risperidone found significantly higher reduction in the first group in negative symptom scores (P = .003) and total score (P = .001). These results measured the time period from baseline to week 8, using the Positive and Negative Syndrome Scale (PANSS). Simvastatin did not significantly differ from placebo for treating schizophrenia in an underpowered study (N = 36).

Two meta-analyses of statin add-on therapy in the antipsychotic treatment of schizophrenia have been conducted. Nomura et al identified 5 randomized controlled trials (N = 236) showing improvement of PANSS total score, but not of PANSS subscale scores. The meta-analysis included studies of atorvastatin, lovastatin, pravastatin, and simvastatin. Risperidone was used in 3 studies; antipsychotic use was varied or not reported for 2 studies. Shen et al identified 6 randomized controlled trials (N = 339) showing benefit for improvement of PANSS positive and negative subscales. The meta-analysis by Shen et al included all 5 trials from the Nomura et al meta-analysis plus an additional trial of simvastatin versus placebo.

Depression, Anxiety, and CVD

Depression1 and anxiety2 have been associated with an increased risk for cardiovascular disease (CVD), independent of psychotropic medication use. This comorbidity is bidirectional, since depression is a common outcome after myocardial infarction and is also associated with higher comorbidity and mortality. In this context, treatment with statins may have an important dual purpose, with benefits to both mental and cardiovascular health. Evidence from a nested case-control study has shown that exposure to statins and aspirin is associated with a reduced risk of de novo major depression.

Atorvastatin, lovastatin, and simvastatin are lipophilic, while pravastatin, rosuvastatin, pitavastatin, and fluvastatin are hydrophilic. The lipophilic statins readily cross the blood-brain barrier. Hydrophilic statins or their active metabolites may also be detected in the brain, although less readily. Laboratory studies have suggested that statins may be neuroprotective against a range of neurotoxic insults, but statins themselves may be neurotoxic at higher concentrations than those obtained at therapeutic doses. The best evidence that statins reduce markers of inflammation is derived from the JUPITER study of rosuvastatin. It is unclear whether brain penetration or reduction in peripheral markers of inflammation is the more important mechanism in terms of potential therapeutic efficacy.

Risk of Drug-Drug Interactions

There is a potential for drug-drug interactions between statins and psychotropic agents (Table 2). Psychotropic agents with lower cytochrome P450 (CYP450) activity should be considered ahead of those with known strong CYP450 activity to reduce the risk of pharmacokinetic drug-drug interactions. Andrade suggests that risks of pharmacokinetic drug-drug interactions between selective serotonin reuptake inhibitors (SSRIs) and statins are negligible at standard therapeutic doses for

Table 1. Statins May Be Beneficial in Treating These Disorders

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<th>Disorder</th>
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Table 2. Investigating Possible Drug-Drug Interactions

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</tr>
<tr>
<td>Fluvoxamine with atorvastatin, simvastatin, or lovastatin</td>
<td>Possible but low</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Significantly interfered with statin therapy</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Did not interfere with statins</td>
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escalolopram, citolopram, and paroxetine with rosuvastatin, pitavastatin, and pravastatin; there is possible but low risk of interactions for combina-
tions of fluvoxamine with atorvastatin, simvas-
tatin, or lovastatin. A study of blood specimens
collected from elderly patients (N = 194) investi-
gated the interactions between statins and antiepi-
leptic drugs, including the mood stabilizers la-
motrigine and carbamazepine. Carbamazepine, but
not lamotrigine, significantly interfered with out-
comes of statin therapy, with lipids reduced for
patients taking either drug but significantly greater
reduction in lipids for those taking lamotrigine. 23
Risks of adverse events may be greater in elderly
cohorts compared to nonelderly individuals.

Antipsychotics may upregulate gene expression of
lipid metabolism pathways, resulting in meta-
abolic side effects, weight gain, and dyslipidemia.
Individuals receiving antipsychotics may have re-
duced response to treatment with statins for dyslip-
idemia, with a common gene variant (SREBF 1) for
a transcription factor in the lipid metabolism path-
way. 24 Dyslipidemia in individuals treated with
antipsychotics may benefit from personalised
treatment plans, in which statins may have an im-
portant but variable role.

In the clinical setting, medication changes, dose
adjustments, and polypharmacy are common in
psychiatric practice and are associated with a
greater risk of adverse effects. Adding a statin to an
existing regimen entails an additional risk that
needs to be considered when the statin is first intro-
duced and whenever there are changes to comedi-
ations throughout the course of treatment. Case
reports on statins and psychotic comorbidities have
identified rare adverse effects of rash, 25 QTc
interval prolongation, 26 and rhabdomyolysis. 27

Concluding Thoughts
Preliminary evidence, mainly from small studies,
suggests that adjuvant treatment with a statin may
be beneficial for individuals taking psychotropic
drugs for depression and schizophrenia. People
with depression, bipolar disorder, and schizophre-
nia are substantially more vulnerable to metabolic
syndrome and earlier age of mortality than the gen-
eral population, predominantly from CVD. Such
medical comorbidities warrant aggressive prophyl-
actic therapy with available agents, in-
cluding statins. Thus, there is sufficient
evidence to suggest that combining statin therapy with antidepressant or an-
tipsychotic therapy may be sensible for
patients with comorbidities when both
pharmacotherapies are indicated. How-
ever, adjuvant treatment with a statin
puraely as an augmentation strategy for
psycopharmacotherapy is still experi-
mental. Although there is a good theo-
retical basis and promising preliminary
data, further research is required, es-
cially larger, multisite, placebo-con-
trolled randomized clinical trials.

Dr Dodd is a principal fellow in the
Department of Psychiatry, University of
Melbourne, a clinical associate profes-
sor at the Centre for Youth Mental
Health and the University of Melbourne, and a
clinical associate professor in the School of
Medicine, Deakin University, Melbourne,
Australia. Dr Gimenez-
Palomo is a psychiatrist in the Hospital
Clinic de Barcelona in Spain and a
researcher at IMPACT, Univer-
sity Hospital Geelong, Australia. Dr
Berk is the Alfred Deakin Professor of
Psychiatry and director of IMPACT, the
Institute for Mental and Physical Health
and Clinical Translation, Deakin
University, Melbourne, Australia.

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Physician Liability During COVID-19: What You Need to Know To Protect Your Practice

Stephanie Sheps

The coronavirus disease 2019 (COVID-19) pandemic has brought a lot of unknowns into the practice of medicine. Doctors are trying to see patients while keeping their patients, themselves, and their staff safe from infection and balancing the threat of being sued for not taking the proper precautions. Stephanie Sheps, vice president of claims at Coverys Specialty Insurance Company, a medical liability insurance provider, shared her thoughts on liability risk in the age of COVID-19 in an interview with Medical Economics.

What are some new liability threats?

There are the obvious risks, including transmission of COVID-19, both to patients and to staff. It is a novel issue because we do not fully understand this virus yet, and things continue to evolve daily. Based on patient and provider awareness and precautionary measures taken to mitigate these risks, I believe that the greatest liability stems from pandemic-related or contextual realms. Pandemic risks are those that do not involve the diagnosis, transmission, or treatment of COVID-19, but are instead related to the changes in how health care is being delivered or not delivered. These risks include the denial of services to patients because of lack of capacity and lack of personal protective equipment (PPE).

Medical visits, especially for checkups and management of chronic conditions, that are deferred or held virtually present some risk. There is a reason we see our providers in person: they get to put eyes on the patient, they get to take labs, they get to really assess the patient using all of their senses. When that is limited by doing visits through telehealth, I think that could present some greater risk in the future.

Are there oversights that make practices more vulnerable to COVID-related lawsuits?

Yes and no. These are common issues that would have existed before COVID-19, like the failure to document informed consent or informed refusal of treatment. Obviously, there are specific risks related to exposure in the office. There are the obvious risks, including transmission of COVID-19, both to patients and to staff. If a deposition is later needed during litigation, you do not want to have to think back to who was working in 2020; you want to have that recorded. If possible, have a video of a day in the life at your facility. It is important, since memories fade, to get a context and to have a living example of how you functioned during this pandemic to illustrate for a jury what it was like to deliver health care during a pandemic.

Remember, the strategy behind tactical risk management is that it is never too late to start. It will be more difficult to gather documents in the future. It will benefit the defense to have all of this information in 1 place, starting with your timeline; then connecting to all of your records and documents; and finally preserving the memories of the actual people who are in charge of those decisions, creating the protocols, and following state federal guidelines with respect to the pandemic.

Do the state legislation protecting businesses from COVID-related lawsuits help medical practices?

Absolutely, they do. The broadest protection comes from the federal extension of the PREP Act, which happened in March of this year. The PREP Act provides immunity to certain individuals, in this case, health care providers, for countermeasures taken to deal with health crises during. Many states have taken the initiative to invoke their own state-related liability protections, and some of those are even stronger, broader, and more encompassing to protect health care providers than the PREP Act itself. There are good protections out there for health care providers, but like anything else, there are ways around them.

What should practices do to minimize their risk from COVID-related legal action?

One of the things that we have been advocating is to continue traditional risk management and clinical risk management practices, and also employ tactical risk management. Those are things that we need to do now in anticipation of the claims we might have to defend in the future. For tactical risk management, we bucket our recommendations into line. In terms of record keeping, make sure that you have documentation, including the purchase of any equipment or supplies, etc. It is also important to have records of patient logs, like when they had visitors, when they left, or dates when the visitation may have been limited or flatly refused.

Document staff training, along with any furloughs and leaves of absence for providers who were concerned about the disease. Maintain a floor plan showing how isolation works for patients that are COVID-19 positive. Also, keep evidence of any guidance on public health and safety measures like wearing masks, by logical extension, may see more claims activity related to COVID-19 because those states are more likely to have more patients who contract COVID-19. Everything, just like the virus, continues to spread exponentially in the states that have passed legislation to help protect businesses from COVID-related lawsuits.

Are there any states or regions where COVID-related actions are more prevalent than others?

Again, it is a little too soon to tell where things are more prevalent because not a lot has been filed in terms of COVID-related lawsuits. We will likely see more case activity in states that do not have specific immunity for COVID-related countermeasures. Some of those are legislated, some of those are by executive order, but those states will probably see more activity. We will probably see more activity in states without tort reform, or states that do not have caps on noneconomic damages. Finally, states that have had limited or no specific guidance on public health and safety measures like wearing masks, by logical extension, may see more claims activity related to COVID-19 because those states are more likely to have more patients who contract COVID-19. Everything, just like the virus, continues to spread exponentially in the states that have passed legislation to help protect businesses from COVID-related lawsuits.

Tactical risk management is that it is never too late to start. It will be more difficult to gather documents in the future. It will benefit the defense to have all of this information in 1 place, starting with your timeline; then connecting to all of your records and documents; and finally preserving the memories of the actual people who are in charge of those decisions, creating the protocols, and following state federal guidelines with respect to the pandemic.

Does the typical malpractice insurance policy cover COVID-related claims?

Typically, yes, a medical professional liability policy covers what we call professional services, which is insurance company lingo for rendering medical care. However, most policies exclude willful or intentional conduct and many also exclude gross negligence.

MS Sheps is the vice president of claims at Coverys. She is also a member of the International Association of Defense Counsel, the Professional Liability Underwriters Society, and serves as vice chairperson of the Professional Liability Foundation of Massachusetts.
Microglial Involvement With Psychiatric Diseases

Haley Alleson Vecchiarelli, PhD, Eva Šimončičová, and Marie-Ève Tremblay, PhD

A complex relationship exists between inflammation and neuropsychiatric disorders, particularly those related to psychological stress exposure, such as anxiety disorders and major depressive disorder. For example, patients with chronic inflammatory conditions (e.g., asthma or arthritis) show a high degree of comorbidity for these and many other neuropsychiatric disorders. There is, perhaps, an evolutionary explanation for this relationship: with sickness, there are a sequelae of behaviors intended to allocate energy resources to deal with the illness, such as drowsiness, anorexia, fatigue, anxiety, altered cognition, anhedonia, along with reduced locomotor activity, social interaction, and exploration. These sequelae appear in rodents and in humans. This behavioral shift is mediated by changes in brain activity among specific regions, including the insula (cortical representation of interoceptive pathways), ventral striatum (reduced reward processing and appetitive motivations), substantia nigra (psychomotor slowing), and dorsolateral prefrontal cortex (cognitive impairment), among others. The neural basis of these and other changes in brain activity and behavior may arise from the diverse activities of microglia, which act as the brain’s resident immune cells.

**Microglia**

Posing as the orchestrators of the defense system in the brain, microglia comprise approximately 10% of its cellular population. Unlike the other brain glial cells, astrocytes and oligodendrocytes, microglia originate from the embryonic yolk sac. They migrate to the brain early in development (embryonic day 9.0 in mice, corresponding to 4 to 5 weeks of human gestation) and self-renew throughout life. Microglia are crucial for the formation and wiring of neuronal circuits during brain development, and for synaptic plasticity as well as learning and memory processes throughout adolescence, adulthood, and aging. Microglia are highly dynamic, and typically exhibit a ramified morphology with processes that constantly survey the brain parenchyma. Their secretion of growth factors supports the maturation of neurons, oligodendrocytes, and astrocytes, as well as axonal growth, myelination, and synapse formation. Microglia-mediated phagocytosis eliminates cellular debris, apoptotic cells, and even synapses in processes such as synaptic pruning. Furthermore, region-, age-, and sex-dependent differences in microglial distribution, morphology, and function in the homeostatic brain have been described in studies. Microglia act as the brain’s primary responders to homeostatic alterations, including stress-induced changes in neuronal activity and synaptic plasticity. Microglia also respond to more global and systemic disturbances associated with altered sleep, inflammation in the central and peripheral nervous system, and dietary imbalance. Exposure to immunological (e.g., viral and bacterial infection), physiological (e.g., trauma, hypoxia-ischemia, disease, or malnutrition), or psychosocial (e.g., low socio-economic status or substance abuse) stressors is associated with altered microglial function and an increased risk of developing a wide range of psychiatric conditions. The vulnerability to these environmental stressors is exacerbated during prenatal, perinatal, and early postnatal development, which are the periods of life associated with the onset of neurodevelopmental disorders. Stress in adolescence or adulthood can contribute to anxiety or depression and potentiate the onset of age-related cognitive decline and neurodegenera-
ative diseases, all of which have an affective component and involve microglial dysfunction. Microglia appear to play a contributory role in the onset and progression of various neuropsychiatric disorders throughout life through abnormal homeostasis maintenance leading to neurodegeneration and synaptic loss.

These are outwardly reflected as cognitive impairments or behavioral alterations, 2 common symptoms of psychological disorders. In both health and disease, microglia exert their effect functions through a variety of mechanisms (Figure 1). As microglia cross the blood-brain barrier, they shape neuronal circuits and maintain brain integrity over the course of life via the a) promotion of oligodendrocyte precursor cell maturation and oligodendrocyte-mediated myelination; b) dynamic scanning of their microenvironment for potential threats or insults using their extensive processes of arborization; c) production of trophic factors to support neuronal maturation and survival, axonal growth and formation of new synapses; d) production of inflammatory cytokines in steady state and increased release with aging or in response to stress/pathological insult; e) and f) active phagocytosis of cellular debris, apoptotic or excessive immature cells and precursors; as well as g) and h) the regulation of synaptic plasticity by active elimination/modification of synapses using synaptic stripping (physical separation of synaptic elements) or synaptic pruning (complement-mediated phagocytosis of synaptic elements/whole synapses). Aging-, stress- or disease-associated alterations of microglia may cause impairment of these beneficial physiological processes and result in neuroinflammation, neurodegeneration, synaptic loss, behavioral changes and/or increased susceptibility to mental diseases in later life stages.

In response to homeostatic challenges, microglia can alter their phenotype and function, thereby adopting a reactive state. Reactive microglia may change their morphology to a hyperpampered or amoeboid shape, upregulate danger associated molecular pattern receptors on their surface and release increased amounts of cytokines and/or other inflammatory factors. Homeostatic challenges are able to prime microglia to intensify phagocytosis and respond more robustly to a subsequent alteration. It was previously thought that reactive microglia exist in 2 states: M1, which resembles a proinflammatory, pathological, and classical reactive phenotype; and M2, which represents an anti-inflammatory, restorative/reparative phenotype. M1-like cells are stimulated by interferon-γ and lippopolysaccharide (LPS) or tumor necrosis factor alpha and express mRNA for inducible nitric oxide synthase and CD86 (a costimulatory molecule). These cells have upregulated phagocytic activity, secrete pro-inflammatory cytokines (eg, interleukin [IL]-1β, IL-12), and generate reactive oxygen species (ROS). M1-like cell functions, which include increased motility, ROS and other proinflammatory mediator production, and membrane turnover, require the following metabolic activities: glycolysis, pentose phosphate pathway activity, nicotinamide adenine dinucleotide phosphate production, and fatty acid synthesis. M2-like cells, on the other hand, are stimulated by IL-4 or IL-13 and express mRNA for arginase and CD206. These cells secrete anti-inflammatory cytokines (eg, IL-10) and growth factors as well as stimulate stem cell production and differentiation. M2-like cells need continual activation to increase the transcription of repair genes as well as produce growth factors, which requires energy production utilizing oxidative phosphorylation (and amino acid/fatty acid oxidation). It is important to note, however, that these classifications, which arose from in vitro cell culture studies, often failed to translate to in vivo conditions. The field thus rejected them. Instead, microglia are now known to adopt various phenotypes, in which they can perform specialized functions, highlighting an important need for more nuanced tools to investigate microglial function. Microglia are heterogeneous: they comprise different subtypes that can be differentially recruited with each adopting different phenotypes depending on the context of health or disease.

Figure 1. Microglial Involvement in Brain Homeostasis

- a) Myelination
- b) Dynamic Surveillance
- c) Synaptogenesis and Axonal Growth
- d) Inflammatory Activity
- e) Clearance of Apoptotic Neurons
- f) Synaptic Pruning
- g) Synaptic Stripping
- h) Postsynaptic

Neuropsychiatric Disorders

AUTISM SPECTRUM DISORDERS (ASD). Abnormalities in social interactions and communication, repetitive behavioral patterns, or sensor and emotional processing impairments—core symptoms of ASD—were reportedly associated with dysfunctions in the neuroimmune crosstalk. People with ASD reportedly exhibit alterations of synaptic density and excitatory versus inhibitory tone, accompanied by a decrease in the expression of synaptic plasticity-related genes and an increase of TSPO signals across multiple brain regions, most notably the cerebral cortex, cerebellum, hippocampus, and amygdala. Results from preclinical studies provided further information on the synaptic changes, their association with impaired neuronal migration, and circuitry formation; and pointed to the role of mutations in microglial...
genes in ASD pathology.5,16 Among these is the gene coding for fractalkine receptor (CX3CR1), which mediates neuronal communication with microglia and is important for their response to stress.16 According to the 2-hit hypothesis of neurodevelopmental disorders, developmental activation of the immune system may act as a first hit, causing microglial pruning, which in vulnerable individuals may result in increased sensitivity as well as inflammatory and phagocytic response to latter stimuli.7 Altered pruning activities of primed well as inflammatory and phagocytic response to individuals may result in increased sensitivity as causing microglial priming, which in vulnerable development of disorders, developmental activities result in inappropriate brain circuit wiring, giving rise to ASD or other neurodevelopmental disorders.7 As an animal model of prenatal infection, maternal immune activation (MIA) is frequently used to study the relationship of inflammation with disorders of a developmental origin.5,16 Obsessive Compulsive Disorder (OCD) and Related Disorders. OCD and related disorders are presumed to result from abnormal wiring in pathways similar to those of TS. Therefore, they share a high degree of comorbidity.17 Review of available data indicates peripheral inflammation and neuroinflammation in patients with OCD, of whom approximately 40% to 50% also suffer from an autoimmune disease of metabolic or cardiovascular character.18 Heightened TSPO binding in orbitofrontal cortex implies increased microglial/inflammatory activity in patients with OCD compared with healthy controls.17 A preclinical model in which there is a selective ablation of a microglial subpopulation from the homeobox protein 8 lineage produced an OCD-like behavioral phenotype.18 Anxiety, Depressive, and Trauma-related Disorders. There is a large degree of overlap in the preclinical models for aspects of these disorders. Many researchers use chronic stress paradigms (social stressors such as intruder, social defeat, or subpar housing), fear learning, threat appraisal paradigms, or reward learning and processing to study precipitating factors or symptoms common across multiple disorders.9 There are numerous reports in animal models of increased microglial density and activity following exposure to chronic stressors. The reports noted morphological changes; increased phagocytosis, notably involved in neuronal circuit remodeling; and secretion of primarily proinflammatory factors.8 These effects, along with associated pathological events (eg, monocyte trafficking across the blood brain barrier), are necessary for driving chronic-stress induced anxiety-like behavior, anhedonia, or learned helplessness.6 Although there is a paucity of postmortem studies in humans, there is evidence of IBA1+ cells as well as upregulation of human leukocyte antigen-D related (HLA-DR; a marker associated with antigen presentation during autoimmunity and infection) in the anterior cingulate cortex of patients with severe mood disorders (including major depressive disorder and bipolar disorder), particularly those who died by suicide.14 In vivo analysis shows mixed evidence regarding TSPO binding in patients with mood disorders, depending on the study and radiotracer.15 Although investigators observed no difference in TSPO binding in patients...
with mild to moderate depression, using a different TSPO tracer in a sample of patients with severe depression showed increased TSPO binding in the striatum, hippocampus, and prefrontal cortex, which related to symptom severity.

Research on the role of microglia in anxiety disorders is quite scarce, particularly in humans. As schizophrenia is associated with over-pruning during adolescence, it is possible that this is due to increased C4-mediated microglial activity. Recent in vitro work, however, found that genetic variations of C4 locus may not be the only contributing factor to this excessive microglial synaptic elimination in patients with schizophrenia.

Microglia also respond to more global and systemic disturbances associated with altered sleep, inflammation in the central and peripheral nervous system, and dietary imbalance. However, a large degree of clinical overlap exists in populations of individuals with depressive and anxiety disorders. There is evidence of increased peripheral inflammation in anxiety disorders, notably associated with increased circulating levels of pro-inflammatory cytokines. These mediators are thought to signal to endothelial cells, but also to parenchymal microglia and astrocytes, resulting in changes in their activity that increase cytokine release, which leads to neuroinflammation (ie, brain correlate of peripheral inflammation). Neuroinflammation may alter neuronal structure and function, which contributes to driving changes in behavior associated with these disorders. However, there are reports of low correlation between brain TSPO binding and peripheral indices of inflammation in humans, confounding this hypothesis.

**SCHIZOPHRENIA.** Both neuroimaging and post-mortem studies highlight alterations of microglia in schizophrenia. Postmortem human samples showed increased numbers of IBA1+ cells, especially with an ameboid morphology throughout the brain. They also showed an elevation of pro-inflammatory parameters. TSPO binding was increased in grey matter across the frontal and temporal lobes of patients with schizophrenia, as well as of those at high risk of developing the disorder. This increase in number and pro-inflammatory activity may be driving an increase in synaptic pruning, which is observed in this disorder.

Results from studies in humans showed upregulation of certain cytokines during prenatal or early postnatal life stages to be involved in the pathogenesis of the disease. Although modeling some of the positive aspects of schizophrenia is difficult in rodents, MIA can be utilized and is associated with elevated brain cytokines, which may potentially alter synaptic formation, refinement, and oligodendrocyte maturation. A more defined link has been demonstrated between microglia and the complement system in schizophrenia. The complement component 4 (C4) promotes synapse elimination, while mice lacking C4 show reduced synaptic pruning. Furthermore, variations in the gene encoding for C4 (resulting in its abnormally increased expression and promoting synapse elimination) are associated with increased risk for schizophrenia.

**BIPOLAR DISORDER.** Evidence that microglia are altered in bipolar disorder comes from PET imaging and post-mortem studies. PET imaging studies showed an increase in TSPO binding in the right hippocampus. However, results of postmortem studies are mixed. A recent systematic review highlighted very few changes. However, there were few studies with decreased levels of HLA-DR, CD68, CD11b, and quinolinic acid (a N-methyl-D-aspartate receptor agonist, which can induce neurotoxicity) in IBA1+ cells throughout the brain, including the dorsal raphe nucleus, frontal cortex, anterior cingulate cortex, and hippocampus. Other evidence shows microglial reactivity in patients with bipolar disorder who died by suicide, but this may be broadly true across diagnoses. Thus, there is currently no consensus as to the role that microglia play in bipolar disorder. It may be that the reduction in reactivity indicates an impairment of synaptic pruning and refinement, as there is no good evidence that bipolar disorder results in a loss of neuropil. Adequate animal models for the mania-associated symptoms of bipolar disorder are lacking, as are models for depressive symptoms, as previously discussed.

**SUBSTANCE USE DISORDERS.** A recent meta-analysis highlighted neuroimmune changes in response to tobacco, alcohol, cannabis, cocaine, methamphetamine and 3,4-methylenedioxymethamphetamine (MDMA), and opioid use. Preclinical work and studies using myo-inositol and TSPO reveal accentuated levels and binding. For tobacco and alcohol, acute exposure leads to a pro-inflammatory phenotype that is reduced with long-term exposure. However, cannabis (which has not been shown to increase microglial reactivity acutely), cocaine, and methamphetamine/MDMA, are associated with increased TSPO binding or myo-inositol levels with long-term exposure.

**Concluding Thoughts.** This article briefly outlines the role that microglia play in neuropsychiatric disorders. For example, there was little discussion of the mediators of these effects (eg, cytokines, neuroendocrine signals) or the influence of infiltrating immune cells (some of which closely resemble microglia in terms of morphology, molecular expression, and functions). Although not discussed herein, how treatments for these disorders may alter microglia deserves discussion. There is some evidence that antidepressants such as selective serotonin reuptake inhibitors reduce microglial reactivity (eg, increased IBA1+ staining) and neuroimmune parameters in rodent models. There are mixed reports of the effects of brain stimulation on microglia (within and outside of neuropsychiatric diseases). An interesting study found that cognitive behavior therapy reduced TSPO binding in patients with depression. Moreover, in patients with psychiatric disorders, add-on therapy with anti-inflammatory drugs such as nonsteroidal anti-inflammatory drugs or minocycline can have beneficial impact on psychiatric symptoms, likely through decreasing microglial reactivity and neuroinflammation. It is clear, however, that more work is needed to understand the role of microglia in current treatment strategies, as well as how they can be leveraged for new treatment pathways.

Another interesting area of growing research is the relationship between the gut-brain axis, microglia, and neuropsychiatric disorders. Particularly at the preclinical level, investigators are looking at the role of the microbiota, the effects of pre- and post-biotics and diet on microglia, and neuropsychiatric disorders. Changes to the gut-brain axis and microbiota can alter levels of neurotransmitters, short-chain fatty acids, and inflammatory signals that can affect the brain (including microglia), which can lead to changes in behavior. This field is still growing, although there is current interest in using pre- and post-biotics as potential therapeutics in neuropsychiatric disorders. Although this review was separated into disorder types, there are changes in brain regions or experiences that contribute to similar symptoms across disorders. Thus, using a Research Domain Criteria (RDoC) approach to investigate the role in the pathogenesis of symptoms may provide insight into a wide variety of disorders. This also highlights the importance of live human brain imaging.

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Full term</th>
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<tr>
<td>C4</td>
<td>Complement component 4</td>
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<tr>
<td>Hdc</td>
<td>Histidine decarboxylase</td>
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<tr>
<td>HLA-DR</td>
<td>Human leucocyte antigen-D related</td>
</tr>
<tr>
<td>IBA 1</td>
<td>Ionized calcium binding adaptor molecule 1</td>
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<tr>
<td>IL</td>
<td>Interleukin</td>
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<tr>
<td>LPS</td>
<td>Lipopolysaccharide</td>
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<tr>
<td>MDMA</td>
<td>3, 4-methylenedioxymethamphetamine</td>
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<tr>
<td>MIA</td>
<td>Maternal immune activation</td>
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<tr>
<td>MRS</td>
<td>Magnetic resonance spectroscopy</td>
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<td>PET</td>
<td>Positron emission tomography</td>
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<tr>
<td>RDoC</td>
<td>Research Domain of Criteria</td>
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<tr>
<td>ROS</td>
<td>Reactive oxygen species</td>
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<td>TSPO</td>
<td>Translocator protein</td>
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Table. Key Acronyms
aging and postmortem studies, as many aspects of these disorders cannot be adequately studied in animal models. However, a recent translational study focusing on microglia-complement signaling in schizophrenia indicated an ability to take clinical findings back to the animal to discover new pathways and mechanisms.

Better and more specific tool development for human imaging studies is crucial, so that we are better able to understand brain alterations that may be driving pathogenesis. Recent advances in the field include new radiotracers that might provide functional insight into how microglia are behaving in different psychiatric conditions, for instance targeting the fractalkine or purinergic systems. The upcoming years are sure to yield new exciting research that will hopefully lead to better targeted and more efficient treatments.

Dr Vecchiarelli is a postdoctoral fellow at the Division of Medical Sciences in the University of Victoria. Ms Šimončičová is a doctoral student at the University of Victoria. Dr Tremblay is a Canada Research Chair (Tier II) in Neurobiology of Aging and Cognition, Division of Medical Sciences in the University of Victoria.

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- Pediatric Collaborative Psychiatrists
- Consultation Liaison Psychiatrists
- Addiction Psychiatrists
- Staff Psychiatrist for Adult Inpatient Unit
- Outpatient Child & Adolescent Psychiatrists
- Geriatric Psychiatrists
- Outpatient Psychiatrists

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**www.pagny.org**

Physician Affiliate Group of New York (PAGNY) provides services to NYC Health + Hospitals Corporation (H+H), the largest public healthcare system in the United States. **EOE M/F/D/V**

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To learn more, contact renee.theobald@HMHN.org or call: 908-839-5693.
UMass Memorial Health Care and the University of Massachusetts Medical School currently have openings within the Department of Psychiatry.

The Department of Psychiatry is a national leader in public sector psychiatry, child and adolescent psychiatry, neuropsychiatry, biological psychiatry, psychosocial rehabilitation, women’s mental health, and addiction psychiatry. We integrate our clinical, research, teaching and community partnership activities to help individuals and families transform their lives through recovery from mental illness and addiction. We are particularly interested in having Faculty join our Department who are motivated for a career in clinical research. We are the largest provider of psychiatric services in central Massachusetts, with over 400 faculty members and 12 hospitals and community mental health centers.

Our residency program trains 7 residents per year, including general psychiatry and specialty tracks for combined adult and child psychiatry and combined neurology. We offer fellowships in Child and Adolescent Psychiatry, Addiction Psychiatry, Forensic Psychiatry, Neuropsychiatry, and Adult Developmental Disabilities. Interested candidates should send their curriculum vitae addressed to Dr. Kimberly Yonkers.

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Psychiatrist, Psychiatric Nurse Practitioner, and Psychologist opportunities available in the following states:

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

Marie Hobart, MD, Vice Chair, Public Sector Psychiatry
marie.hobart@umassmed.edu

Interested applicants should apply directly at https://academicjobsonline.org/ajo/UMASSMED/Psych
(J-1 and H-1B candidates are welcome to apply)
AACP's 2021 Virtual Pediatric Psychopharmacology Update Institute
Beyond One Size Fits All – Predicting Medication Response
February 18-27, 2021
Gabrielle A. Garson, MD, and Jeffrey R. Swann, MD, Co-Chairs

AACP's 2021 Virtual Pediatric Psychopharmacology Update Institute attempts to answer the question: "How do we select the right medication or intervention for the right patient at the right time?" This virtual meeting includes:

• BAMA PRA Gregory J. Creedts™
• A combination of on-demand and live learning from experts in the field
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• Featured presentations addressing how to use precision medicine approaches to select psychopharmacologic treatments based on predictors of treatment response and tolerability

Visit: www.aacap.org/psychopharm-2021 for more information!

AACP’s 68th Annual Meeting
October 25-30, 2021 - Atlanta, GA
James J. McCabe, MD, Program Chair

Submissions to the Call for Papers for AACP's 68th Annual Meeting are due February 16, 2021, or June 7, 2021, for [late] New Research Posters. The online call for papers submission form is available at www.aacap.org/Annual/Meeting-2021. Abstract proposals are prerequisites for acceptance of any presentation. Topics may include any aspect of child and adolescent psychiatry.

For information about all of AACP’s meetings and to register, visit www.aacap.org, email meetings@aacap.org, or call 202.966.7300, ext. 206.

RECRUITING FULL TIME & PER DIEM PSYCHIATRISTS
NEW YORK METRO AREAS

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

TO BOLSTER OUR NETWORK OF OUTSTANDING CARE PROVIDERS,
WE ARE RECRUITING BOARD ELIGIBLE/BORAD CERTIFIED PSYCHIATRISTS FOR THE FOLLOWING POSITIONS:

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ADOLESCENT UNIT
South Oaks Hospital
Amityville, NY

ADULT INPATIENT PSYCHIATRIST
The Zucker Hillside Hospital
Glen Oaks, NY

ADOLESCENT INPATIENT PSYCHIATRIST

The Zucker Hillside Hospital
Glen Oaks, NY

COLLEGE UNIT INPATIENT PSYCHIATRIST
The Zucker Hillside Hospital
Glen Oaks, NY

EMERGENCY PSYCHIATRIST – Per-Diem
Cohen Children's Medical Center, NY

Long Island Jewish Medical Center, NY

OUTPATIENT PSYCHIATRIST
Staten Island University Hospital, NY

CONSULTATION LIASON PSYCHIATRIST
Phelps Memorial Hospital
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Staten Island, NY

Benefits at Northwell Health include:

✓ Nationally competitive salaries
✓ Comprehensive benefits package
✓ Four weeks’ vacation plus paid conference/CME time
✓ Academic appointment commensurate with experience
✓ Advanced education opportunities
✓ College Tuition reimbursement for dependent children

Qualified candidates should forward their CV to Lan Ma: OPR@northwell.edu
Inpatient Child/Adolescent Psychiatrist Opportunities
Child and Adolescent Assessment Units
Cambridge Health Alliance

Cambridge Health Alliance (CHA) (CHA), a well-respected, nationally recognized and award-winning public healthcare system, is seeking a full time psychiatrist for the Child and Adolescent Assessment Units. CHA is a teaching affiliate of Harvard Medical School (HMS) and Tufts University School of Medicine.

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

Qualified candidates will be BC/BE in psychiatry and share CHA’s passion for providing the highest quality care to our underserved and diverse patient population. Please submit CV’s through our secure website at www.CHAproviders.org, or by email to Melissa Kelley at ProviderRecruitment@chaliance.org. The Department of Provider Recruitment may be reached by phone at (617) 665-3555 or by fax (617) 665-3533.

Qualifications:
- Completion of a residency program accredited by the Accreditation Council for Graduate Medical Education (ACGME)
- Completion of a fellowship program accredited by the American Board of Psychiatry and Neurology (ABPN)
- Board certification or eligibility
- Ability to work effectively as part of a multidisciplinary team
- Strong oral and written communication skills
- Demonstrated clinical and research skills
- Ability to work in an environment with high volume and high pressure
- Ability to work independently and as part of a team

Benefits:
- Competitive salary and comprehensive benefits package
- Generous paid time off
- 401(k) and 457 plans (tax defer up to $55,000 per year)
- Health, dental, and vision insurance
- Life, disability, and long-term care insurance
- Retirement plans
- Tuition reimbursement program
- Professional development opportunities
- Work-life balance programs
- Access to cutting-edge technology and research
- Exposure to a diverse patient population
- Opportunities for career advancement

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

We Offer Our Telepsychiatrists The Work-Life Balance They Deserve.

California Correctional Health Care Services is seeking dedicated and compassionate professionals, like you, to join our telepsychiatry team. We offer some of the most advanced technologies available in a clean, comfortable, quiet atmosphere. If you are ready to practice within a special program where you can help change lives, while maintaining the balance in your own, consider joining one of our office-based teams.

**Locations:**
- Diamond Bar
- Rancho Cucamonga
- Santa Ana

In return for your efforts, we offer:
- 40-hour workweek with flexible schedules, (affords you true work-life balance)
- Generous paid time off and holiday schedule
- 401(k) and 457 plans (tax defer up to $55,000 - $52,000 per year)
- State of California retirement that vests in five years (visit www.CalPERS.ca.gov for retirement formulas)
- $10,000 Thank You Bonus to professionals newly hired with the State of California
- Relocation assistance available to professionals newly hired with the State of California
- Paid insurance, license, and DEA renewal
- Visa sponsorship opportunities

Take the first step in joining one of our teams and contact Blair Eversley at (916) 338-3948 or CentralizedHiringUnit@cdcr.ca.gov. You may also apply online at www.cchcs.ca.gov.

Effective July 1, 2020, in response to the economic crisis caused by the COVID-19 pandemic, the Personal Leave Program 2020 (PLP 2020) was implemented. PLP 2020 requires that each full-time employee receive a 9.23 percent reduction in pay in exchange for 16 hours PLP 2020 leave credits monthly through June 2022.

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PSYCHIATRIST
$278,780.51-$339,622.40 annually
7 weeks of annual leave
Full benefits & retirement
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Santa Clara Valley Health and Hospital System, a public healthcare system in the heart of Silicon Valley, is seeking BE/BC psychiatrists & PGY-III/IVs for a variety of clinical settings, including emergency psychiatric services, outpatient behavioral health clinics, and custody health inpatient services. Opportunities for additional moonlighting also exist within our healthcare system.

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

Psychiatrists are eligible for numerous benefits including 7 weeks of annual leave, 1 week of educational leave, 12 holidays, $4500 educational funds, health benefits, life insurance and CalPERS retirement plan. If you are interested in working in a dynamic and collegial work environment, please submit a CV and letter of interest to MD.Recruitment@bhs.scv.org.

The County of Santa Clara is an Equal Opportunity Employer

### Telecare Corporation

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BE or BC psychiatrist needed. Following locations have immediate openings:
- **San Jose, CA**: Schedule: 24 hours per week; Pay Rate: $188 - $230/hour. Excellent Benefits!
- **San Mateo, CA**: Schedule: 24 hours per week; Pay Rate: $192 - $216/hour. Excellent Benefits!
- **Stockton, CA**: Schedule: 24-40 hours per week available; Pay Rate: $144 - $163/hour Excellent Benefits!
- **San Leandro, CA**: Schedule: 40 hours per week; Pay Rate: $188 - $230/hour Leadership Opportunity and Excellent Benefits!
- For additional listings, please visit: [www.telecarecorp.com/physician-jobs/](http://www.telecarecorp.com/physician-jobs/)

You will work as part of a multidisciplinary team. The staff is all very friendly and it is a supportive working environment.

Please email your resume to PoRecruiting@telecarecorp.com

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Manosor Zuberi, M.D.  
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### 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.

*For additional information, please see [Pinnacle Behavioral Health IPA, LLC](#) for further information:

Jessica Wildey, Human Resource Specialist, at 315-765-3359 or [jessica.wildey@omlny.gov](mailto:jessica.wildey@omlny.gov)

New York is the State of opportunity! Join our excellent team of psychiatrists and nurse practitioners delivering compassionate care for patients involved in the justice system through a multidisciplinary model. Central New York Psychiatric Center is a dynamic organization that provides comprehensive, evidence-based mental health services through a continuum of care in our inpatient hospital and statewide correctional facilities and is accredited by The Joint Commission.

**BENEFITS:**
- **Salary Range:** $195,263 - $268,311
- Flexible work schedules. Private practice is permitted
- Potential Tele-Psychiatry positions available at our VTC Suites, including Long Island, Rockland and New York City locations.
- Optional paid on-call duty at the hospital
- Opportunities for academic affiliation with SUNY Upstate, Division of Forensic Psychiatry.
- Generous benefits and retirement package.
- Relocation Assistance.
- Robust continuing medical education opportunities.
- Satellite Units located throughout New York State, within commuting distance of most major cities.

### Psychiatric TMS Center

Pinnacle Behavioral Health IPA, LLC
The Care You Need, The Empowerment You Deserve.

- **Full-time** $300,000.00 - $400,000.00 per year
- *BONUS OFFERED FOR 30+ Hours* Pinnacle Behavioral Health IPA, LLC, a multi-disciplinary mental health practice in Albany, NY, is seeking a full-time (24-40 hours) board certified or board eligible Psychiatrist for their innovative Transcranial Magnetic Stimulation (TMS) center as well as to provide psychiatric services. Here at Pinnacle, we operate one of the only Brainway/Certified Deep TMS machines in the Capital District and are proud to continue expanding our practice through diversifying the types of treatment and volumes of procedures offered by our TMS Center.

Please review our website for further information: [www.pinnaclebehavioralhealth.com](http://www.pinnaclebehavioralhealth.com)

Interested applicants should send a letter of interest and curriculum vitae to [thunt@pinnaclebehavioralhealth.com](mailto:thunt@pinnaclebehavioralhealth.com)

### 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 BHSAdmin@stjohns.org. BHR

### TREATMENTS BEHAVIORAL HEALTH

**The doctors of TRADITIONS BEHAVIORAL HEALTH are the largest provider of MD psychiatric services to adult populations all over California and also now in WA and NV! We provide services to the seriously and persistently mentally ill and have openings in the San Francisco Bay Area, Santa Barbara, San Diego, Los Angeles, Reno and Seattle. Overall we plan to add 50 more Fulltime psychiatrists to bring our medical staff team to 400 psychiatrists. Our packages vary from a minimum of $300,000 per year plus $10,000 in bonuses and a benefit package valued at approximately $90,000, to up to $500,000, for the industrious physician. Our generous benefit package includes up to 6 weeks paid time off per year. If you are creative and think outside the box, if you value diversity and cultural competency, if you like innovative programs that are patient driven, using a rehabilitative, rather than illness model, if you want more time to work with patients, to get the best results, then TBH is the company for you. To learn more about the specific job openings and salary and benefit packages, check out our Website at:**

[www.tbhcare.com](http://www.tbhcare.com) or Email your letter of interest and CV to our company VP of Recruitment, Derek Sawyer at: Derek@tbhcare.com

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The duloxetine your patients require—approved in a sprinkle formulation designed for those who cannot or will not swallow solid forms of medication\textsuperscript{1}

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**IMPORTANT SAFETY INFORMATION (cont’d)**

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

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

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

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**IMPORTANT SAFETY INFORMATION [cont’d]**

**USE IN SPECIFIC POPULATIONS [cont’d]**

- **Lactation**: Advise breastfeeding women using duloxetine to monitor infants for sedation, poor feeding and poor weight gain and to seek medical care if they notice these signs

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

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**References:**


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