The Movie on Your Patient’s Mind

Harvey R. Greenberg, MD

I thought I’d pondered every possible psychological aspect of cinema, when it occurred to me that I’ve never addressed how to treat a patient’s mentioning a movie. Hence the following.

Context would obviously dictate your response. Most patients refer to a movie in passing (eg, during a short medication check appointment). Re-answering with a companionable murmur usually suffices. However, always be vigilant when clients mention a film during psychotherapy, no matter how briefly, especially a specific scene, shot, or quote, even a musical theme. Here, deeper delving—free and directed associations, etc.—may yield useful, even profoundly healing insights.

A flat disclaimer that you’ve already seen a film can be as off-putting and dismissive as stating you’ve already heard a joke. You aren’t performing brain surgery; but primum non nocere still pertains—even with new, sensitive patients.

Protect your therapeutic alliance by refraining from criticizing or praising a film, lest you unintentionally give offense. Even when I know a patient well, I don’t share my opinion unless it might be helpful.

(continued on page 24)
FROM THE EDITOR
Looking at the Past and Forward to the Future
John J. Miller, MD | Editor in Chief

I am excited and appreciative to begin my new role as Editor in Chief of Psychiatric Times. First, I would like to thank the Psychiatric Times editorial staff, including Executive Editor Natalie Timoshin, Editor Heidi Anne Duerr, MPH, and Digital Managing Editor Laurie Martin, for inviting me to this position, and believing in my ability to serve in this role. Also, I would like to thank Allan Tasman, MD, and Michelle Riba, MD for their time, efforts, and thoughtfulness during their tenure as Editor in Chief and Deputy Editor during the past 4 years.

Since its inception in January 1985, when it was founded by John L. Schwartz, MD, Psychiatric Times quickly became the favorite and most-read psychiatric publication for the front-line clinician. Due to the wise and insightful guidance and stewardship of its first three Editors in Chief, John L. Schwartz, MD, Ronald W. Pies, MD, and James L. Knoll IV, MD, it has continued with statements of accomplishment and mastery, only to be upended as new discoveries force us to rewrite the old textbooks. The first version of the Periodic Table of the Elements was attributed in 1869 to Dimitri Mendeleev, which seemed to provide the explanation of physical reality. Although a major scientific accomplishment, science at that time was unaware of the existence of electrons and neutrons.

One of the foundations of modern physics is the electromagnetic spectrum of radiation. Before 1800, we were only aware of visible light—that small part of the spectrum we can see when light passes through a prism—ranging in color from red to purple. It was only in 1800 and 1801 that the spectrum was found to be broader, to include the infrared and ultraviolet. Finally, in 1895 the German physicist Wilhelm Röntgen “stumbled on X-rays while experimenting with Lenard tubes and Crookes tubes.” Subsequently, the entire electromagnetic spectrum was established, which ranges from gamma rays to radio waves. At the time of each of those monumental discoveries, scientists believed that they had finally figured out the nature of reality.

More pertinent to the present time is the continuing unravelling of the relationship between genes and disease. In 1953 James Watson and Francis Crick proposed that the structure of DNA was a double-helix, and a few years later correctly predicted the information flow from DNA to RNA to proteins. Biologists and chemists celebrated this discovery that will transform our practice of psychiatry—as this can be said of any time in the past. Science is growing as this can be said of any time in the past. Science is growing.
Malpractice Marathon

Continued from cover

On the afternoon of June 1, “Mr S” was brought to the ED. A divorced man in his forties previously unknown to me, he had had earlier admissions, including at least one to the state hospital. Unfortunately, he had never pursued the necessary interim treatment. Aware that he was becoming ill, he went to his sister’s house where his behavior became erratic and violent, ending in his breaking a window. He was taken to the hospital by ambulance.

In the ED, he was combative, requiring physical restraint and repeated injections of haloperidol. After he was admitted to the psychiatric ward, I was called as the attending physician.

He was quite sedated and unable to converse coherently when I saw him the next day. Laboratory results taken on admission showed a high creatine kinase (CK) level but were otherwise unremarkable. He also intermittently exhibited muscular stiffness and mutism. His physical examination revealed a loud, strange sound in his chest that I could not identify, and I requested an internal medicine consultation.

Mr S was transferred to a medical ward. After a neurology consultation the next day, he was returned to psychiatry on the assumption that he was experiencing extrapyramidal symptoms. The consultant also mentioned that the clinical picture was “something suggestive of neuroleptic malignant syndrome” (NMS). A then-recent journal had devoted an entire issue to NMS with a cover drawing of a patient in flames, encaised in wood. Certainly dramatic but nothing like Mr S, who didn’t have severe muscle rigidity or a temperature higher than 101.

The high CK level was not fully explained, but he had struggled against the restraints in the ED and had received several intramuscular injections, which could account for this. He had also cut his hand while breaking the window. Blood levels were measured daily and fell to a normal range over several days. Medications were initially withheld to allow him to be more engaging and able to respond during the interview.

My partner was taking over next month, and I would be leaving. This looked like my last big case, and I was determined to do this properly, without the usual time pressures. I obtained as many medical records as possible, interviewed family members, and spent time every day—sometimes twice daily—speaking with Mr S as he became less sedated from the medication administered in the ED. With the information obtained, his diagnosis appeared to be psychotic mania.

Unfortunately, without antipsychotic medication, Mr S became increasingly delusional, fearful, and uncooperative. A series of medications was tried over the initial 2 weeks but were either poorly tolerated or ineffective. On the third hospital day, he expressed the belief that he was possessed by the devil and was being visited by his dead grandfather. On day 4 he said he felt fine and wanted to go home but then wondered aloud if he was alive. On day 8 he loudly announced that he was the “Second Coming” and made numerous calls to the police on the patient phone. He questioned himself in the bathroom and had to be physically extracted when he refused to come out.

Hearing airplanes in the glide path to the airport near the hospital, he thought the sound heralded the end of the world. He was found alone in his room at one point with his arms outstretched against the wall in the form of a cross, whispering, “Jesus.” At 2 AM on the 9th day, the patient was in the shower screaming, “**the devil,**” refused to come out, and was physically removed and placed in a seclusion room.

After 2 difficult weeks, Mr S began to improve with chlorpromazine without significant adverse effects. When seen on the 15th day, he was calmer, less suspicious, and more accessible. On the 16th day, as I sat at my office desk doing administrative work, I received a phone call from the ward reporting that Mr S had been found dead in his bed an hour after he was last checked. My initial reaction was disbelief and shock, and I thought they were speaking about another patient or to the wrong doctor.

His sister, the head of the family, was the officer manager of a surgical colleague. As soon as the office opened, I went to inform her, not wanting some impersonal clerk to deliver the news. I later met with Mr S’s brothers, but it was difficult to explain that I had no idea why he had died—this, they could not accept.

Life went back to normal and I left the hospital, as planned, shortly thereafter. Eighteen months later, a lawsuit was filed. I learned of it on the radio driving home from work and was soon contacted by the newspaper for which I had no comment. The contention was that the death had been caused by NMS. This made no sense as patients with NMS do not die quietly in their sleep; they die in extremis in the ICU. I was assigned an attorney by my insurance carrier, and we went to work.

The next step was the medical claim conciliation panel, a procedure designed to discourage spurious malpractice suits consisting of an attorney and two physicians in a kind of casual trial-like atmosphere to determine if there was merit to the suit. Their conclusion was that there was not—but this was advisory only, not binding on either side and could not be mentioned in subsequent proceedings.

This did not deter the plaintiff and a trial date was set. The plaintiff’s attorney was a young, “cobby” personal injury lawyer who was eager for his first big win in what he would term at trial, “a death case.” Then came interrogatories, written questions from the plaintiff’s attorney requesting answers to a wide variety of questions and very time consuming, one of which was to list every book in my professional library, which covered an entire wall of my office. Fortunately, my lawyer replied that we would not respond to that.

It was then time for my deposition, based partly on earlier interrogatories. The plaintiff’s attorney was eager, inexperienced, and animated, and the deposition was, at best, disorganized and took the better part of the day. There seemed to be no clear structure or goal, just a series of random questions, many of which demonstrated a lack of knowledge on the subject. I was exhausted.

Four years later, the trial was held. Malpractice cases are not easy to win and depend heavily on expert testimony. Physicians are at something of an advantage in that they know who the real experts are, even if they are not full-time forensic practitioners, while inexperienced plaintiff’s attorneys do not. It could not have been truer in my case. I was able to find and hire an academic psychiatrist engaged in NMS research who had written the only book on the subject. His opinion was that Mr S indeed had early NMS but that it had quickly dissipated and it certainly had not caused his death. NMS typically leaves no identifying evidence at autopsy. As in any field, experienced experts can identify early, partial signs of problems undetected by the inexperienced and, given the moment in history, I doubt one in a hundred competent psychiatrists would have been able to make the diagnosis at the time.

The trial took just over 3 weeks, punctuated by the judge’s need to take a week off for personal matters. Late in the trial, we were required to attend a settlement conference with a very pleasant, retired judge but without the plaintiffs, who had generously offered to accept the $2 million limits of my malpractice insurance. The judge urged us to do so. We declined.

Deliberation took several days, marked by numerous additional questions by the jurors before a decision in my favor. I bought my attorney some expensive wine and went home. Life returned to normal.

Unbeknownst to me, the plaintiffs were dissatisfied with the verdict and had appealed the case. Thirty items were submitted, one was upheld, “failure to provide informed consent.” Instructions as to how to do this with a disorganized, delusional person were not included.

A new deposition was based largely on the extensive list of interrogatories I had answered 13 years earlier but had not reviewed since. Running through the list, the plaintiff’s attorney had certainly climbed the learning curve, but there seemed to be nothing new until the question of how informed consent had been determined. Thirteen years ago, I had answered the question, “Absent refusal, consent is assumed.” It literally took my breath away, and I had to call for a recess.

Seven years to the month after the first, the second trial began. I had a new lawyer because the first lawyer had retired; and they had a new expert. The nature of the complaint at issue meant that the entire case would need to be re-tried. The new expert was an academic forensic psychiatrist who had never seen a case of NMS but whose expertise lay in the area of informed consent.

This trial, also lasted just over 3 weeks, but the jury took less than an hour to decide in my favor. Later, several jurors reported that they would have announced the verdict sooner but had not wanted to appear cavalier. On this occasion there was a nice, relaxed dinner with my wife and attorneys. There would be no further appeals.

Dr Betwee is a retired psychiatrist.
Duty of Care and Informed Consent

James L. Knoll IV, MD

Medical malpractice, a form of professional negligence, remains a heavily criticized legal solution for ensuring patient autonomy and competent health care. From caps on damages, to alternative dispute resolution, to so-called “communication and resolution programs,” the main concerns have included: unfairly exposing physicians to hindsight bias, stifling medical progress, and encouraging “defensive medicine.” Psychiatrists’ concerns about medical malpractice claims can affect the way in which they deliver care. When a psychiatrist is the target of a malpractice claim, the stress involved may produce intense feelings of shame, anxiety, and depression. Although only 2.6% of psychiatrists face a malpractice claim each year (the lowest among medical specialties), about 16% will be sued for malpractice at some point in their careers.1,2

With the series Psychiatric Malpractice Grand Rounds, our objective is to provide constructive, educative, and pragmatic pieces on the subject of psychiatric malpractice. Readers should feel free to submit their cases and/or questions with the expectation of collegial and respectful responses. Those who submit are welcome to use their own name or submit with a request of confidentiality. Our goals are to reduce stress by offering psychiatrists knowledge about a typically unfamiliar subject, and exploring the limits of psychiatric standards and certainty. Our responses cannot be considered legal advice or a complete analysis of any case. Rather, we hope to choose cases that present common themes seen in psychiatric malpractice cases that allow for optimal learning.

Duty of Care

In his Portrait of a Psychiatrist piece, Dr. Jon Betwee graciously allows us to learn from his lapsed table experience of back-to-back malpractice cases, which initially raised the specter of neurolologic malignant syndrome (NMS).

In a medical malpractice case, to prevail a plaintiff must prove by a preponderance of evidence the four “Ds”: Duty of care to the patient, but Deviation from the standard of care—which Directly caused the patient’s Damages. Thus, even if we assume that NMS “caused” the patient’s death, the plaintiff would still need to prove that this directly resulted from Dr Betwee’s deviation from acceptable standards of care. Based on the author’s description, it appears that evidence was insufficient to prove that NMS played a causal role in the patient’s death.

Neuroleptic Malignant Syndrome

NMS is typically characterized by the tetrad of fever, mental status change, rigidity, and dysautonomia. Ever a fan of medical mnemonics, I like to remember the acronym “RAD” for NMS symptoms:

- Rigidity: “lead-pipe” rigidity or cogwheel rigidity
- Autonomic instability: tachycardia, labile or high blood pressure, fever (typically higher than 100.4°F [38.0°C], although fever may be delayed or sometimes absent)
- Delirium: reduced or fluctuating level of consciousness

It is important to keep in mind that the presentation of NMS can vary substantially. The incidence of NMS is approximately 3% or less among patients taking antipsychotic medications.3 Mortality due to NMS is usually a result of the autonomic instability and related comorbid medical problems. The mortality rate is about 5% to 20%.

This represents a substantial decrease from early NMS reports in the 1960s when the rate was as high as 76%.4 It seems likely that greater awareness, earlier identification, and more aggressive treatment are responsible for reduced mortality rates.

Symptoms of NMS may occur after a single dose of antipsychotic or after many years of treatment. Most research suggests a recent or rapid dose escalation, or an abrupt switch from one medication to another, can increase the risk of NMS.5 Other risk factors associated with NMS are acute catatonia, extreme agitation, use of lithium plus an antipsychotic, higher potency antipsychotic medication, and lithium plus an antipsychotic medication.3 Mortality due to NMS is approximately 3% or less vary substantially. The incidence of NMS is usually a result of the autonomic instability and related comorbid medical problems. The mortality rate is about 5% to 20%. This represents a substantial decrease from early NMS reports in the 1960s when the rate was as high as 76%. It seems likely that greater awareness, earlier identification, and more aggressive treatment are responsible for reduced mortality rates.

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chotics, depot antipsychotics, and dehydration. Successful treatment of NMS requires identifying and stopping the causative agent and implementing supportive care (eg, rehydration, ICU level care if necessary). In severe cases, the use of dantrolene, bromocriptine, or amantadine may be warranted. It is also reasonable to treat NMS emergently with a benzodiazepine along with dantrolene or bromocriptine. ECT is also a reasonable treatment consideration, yet prospective, randomized controlled studies are lacking. While most episodes of NMS resolve within 2 weeks, negative prognostic risk factors can include depot antipsychotic use and underlying structural brain disease. Nevertheless, most patients recover without sequelae if there has been an absence of significant hypoxia or hyperthermia for extended periods.

Analysis
Returning to Dr Betwee’s case, it is a fact that the vast majority of malpractice cases settle or resolve before a trial, and the deposition of the defendant doctor can play a key role in the outcome. Dr Betwee raises two points regarding malpractice depositions I would like to address. First, he notes that plaintiff’s attorney seemed eager, inexperienced, and animated, and the deposition was, at best, disorganized and took the better part of the day. This may indeed be the case; however, I would humbly offer that my psychiatric colleagues are not too quick in dismissing similar circumstances. Skilled attorneys have different styles and strategies. The clueless, eager presentation may merely disguise a well-planned strategy to lower the defendant’s guard, thereby disguise a well-planned strategy to approach a patient’s medication administration. A seemingly random or unstructured approach to questioning may make treatment decisions, all too often, unpredictable and confusing. Good questions about. Instead, the defendant psychiatrist should seek to have the deposition somewhere else, such as an attorney’s conference room, a hotel conference room, or some other neutral venue.

Informed consent
Dr Betwee’s second suit focused on the critical issue of informed consent. Breach of informed consent may be actionable as battery or as malpractice. The legal development of informed consent has stressed the functionalist model of competence, which holds that the individual’s capacity is determined by demonstrable abilities as opposed to diagnoses or psychiatric labels. In obtaining authentic informed consent from patients, it is important to assess whether they possess the following: the ability to understand information relevant to the decision; the ability to appreciate the situation and its consequences; the ability to apply the relevant information rationally; the ability to communicate a stable, voluntary choice.

Guidelines have been developed for assessing a patient’s competence to make treatment decisions, although currently, use of such tools in most clinical practice would exceed the standard of care. The MacArthur Competence Assessment Tool (MacCAT-T) is one of the most recognized guidelines and contains standard questions that focus on the four main areas of treatment capacity. The prescribing clinician should first strive to approach a patient’s medication administration as a clinical problem. Many incidents of treatment refusal are not due to a lack of treatment capacity, but rather to a host of other clinical factors such as poor therapeutic alliance, inadequate time spent with the patient, objection to specific medication adverse effects, previous bad experiences with treatment, and fear of the stigma of receiving psychiatric treatment.

Dr Betwee faced a perplexing challenge—how to obtain informed consent “with a disorganized, delusional person”? Depending upon the severity and nature of the symptoms, it may be more helpful to reframe the question as how can one ascertain, via evaluation, whether the patient’s symptoms preclude him or her from demonstrating competence to make treatment decisions? Although Dr Betwee assumed consent because “absent refusal, consent is assumed,” there was enough supporting evidence to allow the jurors to find Dr Betwee’s favor. In general, however, the mere absence of a patient’s refusal on its own, does not allow the psychiatrist to conclude “consent is assumed.”

Legal perspective
It is important to distinguish between assent to treatment and informed consent. Assent merely means willingness to accept treatment—the patient may or may not have the capacity to make a decision about the type of treatment. In other words, the patient acquiesces to treatment without having true legal capacity. In contrast, informed consent means that the patient has legal capacity to make a decision about treatment. The US Supreme Court addressed the issue of consent versus assent in Zinermon v Burch when it held that a psychiatrist’s patient’s constitutional rights were violated when he was allowed to sign into the hospital voluntarily—yet was incompetent to give informed consent to do so.

Some further details about Zinermon v Burch may be enlightening. Darrell Burch was found by police wandering along a Florida highway in bad shape. He was taken to a mental health facility where he was found to be bloodied, bruised, hallucinating, confused, and believed he was “in heaven.” Burch was asked to sign forms giving his consent to admission and treatment, which he did. He remained at the facility 3 days, and received a diagnosis of paranoid schizophrenia (and was treated with antipsychotic medication).

It was later determined that Burch needed continued hospitalization, and he was referred to Florida State Hospital (FSH). Upon referral, he signed forms requesting voluntary admission. Once at FSH, under Dr Zinermon’s care, Burch signed additional forms for voluntary admission and treatment. The forms contained the proviso that his voluntary admission would be “in accordance with the provisions of expressed and informed consent.”

At FSH Burch was confused, unable to state the reason for his hospitalization and still believed that he was “in heaven.” Subsequent records describe Burch as extremely psychotic, paranoid, and hallucinating. After 5 months of treatment, his symptoms improved. However, there was never a hearing regarding his hospitalization and treatment.

After his release, he complained that he had been admitted inappropriately and did not remember signing voluntary admission forms. Burch filed a civil rights suit alleging that he was incompetent to give informed consent, and the failure to initiate Florida’s involuntary commitment procedure denied him constitutional- ly guaranteed procedural safeguards. Ultimately, the Supreme Court held that it was foreseeable that persons requesting treatment might be incapable of informed consent, and only hospital staff are in a position to ensure that proper procedures and safety guards are afforded to those unable to give consent.

In a scholarly critique of Zinermon, Winick believes the decision was correct; however, the opinion contains broad dicta that, if followed stringently, could undermine the therapeutic advantages of voluntary admission and convert the voluntary admission process into a form of involuntary commitment. Winick argues that the need for a hearing should be limited to facts similar to Zinermon—a grossly incompetent person seeking admission. That is to say, the mere fact that an individual seeking voluntary admission is mentally ill and in need of hospitalization should not rebut the presumption of competence. Research on decision-making capacity has suggested that many individuals hospitalized with mental illness do possess competence.

Dr Knoll is Director of Forensic Psychiatry and Professor of Psychiatry, SUNY Upstate Medical University, Syracuse, NY.

References
Psychiatric Times will be at the APA Annual Meeting! Drop by for a chat with editors and authors. Meet publishers and partners. **Booth #1424.**

Questions? Contact Natalie Timoshin at natalie.timoshin@ubm.com
The Complexities Behind the Act of Suicide

**Andrew Campbell-Watt**

I am a 78-year-old retiree, living in Australia. I notice that there have recently been a few articles about the contentious subject of suicide in *Psychiatric Times*. My first wife died from suicide about 40 years ago, and my second wife died 3 years ago after a short illness.

Some people do commit suicide, and this has surely happened since humans first walked the earth. This is not a treatise on the causes or possible reasons for suicide, but the complexities behind the act have puzzled me for many years. In particular, our seeming abhorrence and our obvious dismay, regret, and great sadness that anyone should even contemplate the need to end their life, by whatever means has taxed my understanding and the meaning of my life.

What follows below is my considered opinion.

I ask the question—why is suicide considered such a bad thing? Now I am not advocating that anyone should commit suicide. I am just trying to pick apart the emotional clutter that accompanies this very personal and private act. The only answers I get are that it is a waste of a (usually) young person’s life; that they were loved; that they had unlimited potential, now never to be realized; that they had a future to live for . . . etc, etc.

This is partially correct but is not a real answer. The person concerned—the person now deceased—obviously had a different view of life. I am not discussing his or her view—I have no idea what that was. I am discussing our view—that of the outsider—the ones left behind.

Why are we “outsiders” (I deliberately use this word because we are “outside” that person’s inner world) afforded because someone considers living—in their current situation—to be so bad, so threatening, so limiting as to be not worthwhile continuing? Are we discomfited because this rejection, this dismissal of all we have striven for (in “our” world), may reflect poorly on us, those left behind, regarding the way we have organized the world? Are we disturbed by the confronting prospect of having to admit that we make mistakes and that the way in which the economy, our legal, welfare, and education systems are set up may actually cause distress, that we are not always fair or just in our dealings? Do we feel guilty that we have developed a financial system that promotes the massive imbalance between the very wealthy and the very poor and the disadvantaged?

We have to recognize that we are all, all, party to the ills of the world. We created them. If we look with even a modicum of insight, we should see in ourselves the cause of these short-comings and see ourselves reflected in the eyes of the distressed. And we should be dismayed.

Is this why we consider suicide a “bad thing” and are so shocked when it occurs?

It is needful to remember that we, each one of us, have our own experiences of life. These are our own. No one can see the world through our eyes with the same imagery and emotional response. No one can see the world through our eyes with our life experiences and our interpretations of those experiences—these are our own.

**READ MORE ON THIS TOPIC**


So, I ask the question again—why is suicide considered such a bad thing? Obviously for the person concerned the prospect of death is more alluring than continuing living as currently experienced. What is “wrong” with that? It is their choice.

Then, for some to say that only God can decide when or where a person dies is surely a gross over-...

“**It is no measure of health to be well adjusted to a profoundly sick society.**”

Jiddu Krishnamurti (1895–1986)

(Continued on Page 25)
Climate Disruption and the Psychiatric Patient

By Burns Woodward, MD

Stормs, floods, and fires caused by human-generated global warming correlate with elevated rates of anxiety, depression, and suicide.1 In the longer term, stress- and loss-related psychiatric disorders result from climate-related physical illness, economic disruption, migration, and violence. Limited coping skills and reduced socioeconomic resources make psychiatric patients especially vulnerable to these effects. In day-to-day practice, however, it can be difficult to connect these large-scale events with the treatment of individual patients. Identifying patients at risk for the psychiatric effects of climate disruption provides guidance to clinicians as they address these issues in treatment.

Differences in exposure and coping

The impact of climate disruption on a patient’s treatment is determined by the individual’s exposure to climate-related problems, psychiatric symptoms, resources, coping skills, and readiness to address the risks he or she faces.

Patients who experience distressing or disabling anxiety, depressive rumination, or delusions about climate disruption have diagnosable psychiatric disorders. Such patients need treatment with psychotherapy and/or medication. But some patients with such symptoms also face actual dangers, and treatment is likely to be more effective when the risks they face are considered. Cognitive therapy can distinguish realistic dangers from the catastrophic thinking associated with pathological anxiety and depression. Behavioral interventions to curb internet searches, calls to public officials, and hounding of family members about energy usage can limit symptom aggravation.

Symptom management alone, however, can be maladaptive when there is actual danger. A patient with obsessive-compulsive disorder may need to limit exposure to climate-related news and manage his anxiety about CO2 emissions enough to keep his home warm. But acknowledging his children’s vulnerability to wildfire-associated respiratory illness might motivate him to participate in an advocacy group where social feedback could channel his anxieties toward meaningful steps to reduce his family’s risk.

Patients who have experienced heat waves, wildfires, floods, or other climate-related emergencies may, as the first priority, need guidance about dangers they continue to face. The US Centers for Disease Control and Prevention (CDC) provides information about reducing harm from heat, smoke, and water pollution.2–4 Patients with severe and persistent psychiatric illness are especially vulnerable to these risks because of poor self-care, medical conditions, and medication.

After such disasters, psychiatrists are also likely to see patients suffering from trauma-related disorders and depression as well as exacerbations of pre-existing mental and addictive disorders. After the acute trauma is addressed, clarifying the connection between the patient’s symptoms and weather-related events can lay the groundwork for anticipating and preparing for the next emergency. Moving from viewing the disaster as an unpredictable act of God, for example, to an expected consequence of global warming may free the patient to plan for future disruptions of access to food, water, medication, and treatment, as well as the possible need to evacuate. This can be a step on the path from helpless vulnerability to self-efficacy.

Those living or working in areas at risk for climate-related disasters also benefit from emergency planning, but clinicians may first need to address their patients’ apathy. This appears in many forms—outright denial of risk, belief one is invulnerable, projection of responsibility onto government officials or corporations, exaggerating the efficacy of ameliorative measures, “traditionalist” refusal to change, focusing on immediate problems, or fatalistic passivity.5 When these resistances are addressed, patients will be more able to face the tragedy of their situations.

No region is free from risk—residents of non-coastal New England, for example, may feel complacent in their low vulnerability to wildfires and storm surges but ignore dangers from heat waves, inland flooding, and vector-borne diseases.6 Patients may be open to discussing these risks during periods of severe local weather or news of climate-related events elsewhere.

Warning about danger, however, can be counterproductive when it elicits defensiveness, guilt, or anger.3 In the words of the climate scientist Susanne Moser:

People need a minimum amount of information, a realistic assessment of the threat or diagnosis, a sense of personal control over their circumstances, a clear goal, a clear understanding of the strategies to reach that goal (including the possible setbacks along the way), a sense of support, and frequent feedback that allows them to see that they are moving in the right direction.3–7

This is clearly more than can be accomplished in a single interview; clinicians may need to view their work as a series of steps to help patients change. Motivational interviewing techniques—open-ended questions, reflective listening, summarizing statements, and supportive comments—facilitate collaborative evaluation of risk and planning for safety.

Some patients experience deeper anxieties related to loss of an expected future for themselves, their progeny, or the human species. Others grieve for familiar natural environments or for nature in its sense of an ultimate home.3–7 Especially vulnerable are those who have devoted personal or career resources to fighting climate change. Such “climate activists” may become despondent with news of further climate degradation or political events that threaten the environment. While some such patients are depressed, others are better characterized as suffering from a form of existential despair. A related issue is psychic numbing. This differs from the apathy associated with failure to understand climate disruption. Numbing occurs when the individual perceives the threat but feels powerless and gives up.
While symptoms of climate-related despair overlap with those of depression, the distinction is worth making, since treatment may differ. DSM-5 provides some guidance in a footnote about the differences between grief and depression. Extrapolating from this to climate-related dysphoria generates several distinguishing features, which are summarized in the Table.

Affect in climate-related despair comprises feelings of emptiness, loss, and meaninglessness, while clinically depressed patients are depressed and anhedonic. Climate-related despair may be limited in scope: patients may still experience humor and joy about other subjects. Depression, on the other hand, tends to be persistent and pervasive. Individuals suffering from climate-related despair are preoccupied with climate issues and ideas of a diminished future, while in depression thoughts tend toward guilt and hopelessness about one’s own life. Self-critical thoughts in climate-related despair usually involve failure to achieve climate-related goals (eg, passing a carbon tax bill). Self-esteem is generally preserved in climate-related despair, while depressed patients experience self-loathing and worthlessness.

There is no research to support pharmacological treatment of climate-related despair. When clinical depression is present, antidepressants are likely to be useful, since they can be effective for depression in other situations of danger and loss, such as palliative care. We have no treatment manuals or clinical guides to guide psychotherapy of climate-related despair, but a growing body of evidence supports meaning-based psychotherapy in other tragic situations. Such therapies typically combine various techniques, including mindfulness and cognitive-behavioral therapy, to help patients accept difficult situations and unpleasant emotions and to engage in activities that promote their personal values. One such approach, Transformational Resilience, addresses the psychosocial effects of climate disruption at both individual and community levels.

The challenges for therapists include hearing, containing, and working through patients’ despondency while monitoring for depression, which might require additional treatment. The goal is to convert such despair to what has been called tragic, or active, hope—a positive orientation toward the future despite ongoing recognition of danger and loss.

A key element in such psychotherapy may be the clinician’s role in containing the patient’s dysphoria, anxiety, and trauma symptoms during the search for a path toward meaning and hope. Moving beyond grief to behavior that furthers personal values is likely to promote healing. Some patients may progress from acknowledging danger and loss directly to action without explicit grieving, but therapists are wise to keep in mind their possible need to express unacknowledged dysphoria. Some patients may benefit further when they go beyond individual energy conservation and personal risk reduction to engage with others—by discussing climate issues, participating in community groups, advocating for governmental action, and supporting businesses and organizations that take constructive measures.

**Clinicians’ reluctance**

Psychiatrists may doubt the connection between climate disruption and psychiatric disorders. The evidence is increasingly strong, and Hayes and colleagues have recently published an excellent critical review that is free on PubMed.

Others may view climate-related mental health issues as beyond the scope of psychiatric practice. Making climate disruption the focus of every patient’s treatment would be highly inappropriate, but for many patients, addressing these issues is likely to save lives and improve treatment responses.

Climate disruption is now so politicized that clinicians may fear they will be viewed as advocates or offend patients. While political campaigning in the psychiatric office is inappropriate, effective treatment includes addressing public issues that impact patients’ treatment in clinical terms that emerge from patients’ needs and goals. We address controversial topics such as gun ownership as they relate to patients’ mental health, and we can do the same for climate-related issues.

Psychiatrists may need to address their own fears and despair about climate disruption. Such emotions can lead to avoiding discussion of climate-related issues or approaching the subject in ways that elicit fear or guilt. Recognizing that climate disruption is already occurring, future problems are inevitable, and the problem is global, psychiatrists may believe their own and their patients’ efforts are insignificant. In the end, however, climate problems will be addressed by individual human beings becoming educated and making decisions to act within their areas of influence—at the individual, community, corporate, governmental, and global levels. Addressing climate issues as they affect psychiatric patients advances global change, one patient at a time.

**Conclusion**

Like other citizens, psychiatrists can educate themselves about climate problems and reduce their carbon footprints. They can prepare their practices for climate-related events by arranging secure and accessible storage of records and making plans for communication with patients during emergencies. They can advocate for similar actions by hospitals, mental health agencies, and professional organizations. They can participate in APA District Branch disaster preparedness committees, the APA Caucus on Mental Health and Climate Change, and the Climate Psychiatry Alliance.

Discussing relevant aspects of climate disruption with individual patients can reduce their exposure to harm. In some cases, it will improve treatment responses. Addressing the paralysis associated with climate-related despair can increase both clinicians’ and patients’ sense of agency in dealing with problems they perceive as out of their control. I have a mental checklist I review annually with each of my patients, which includes screening for tardive dyskinesia, laboratory monitoring for medication adverse effects, smoking status, firearm safety, and contraception. Climate disruption is now on that list.

**Dr. Woodward** is a psychiatrist in private practice in Waban, MA.

Dr Woodward reports no conflicts of interest concerning the subject matter of this article.

**References**


**TABLE. Distinguishing climate-related despair from clinical depression**

<table>
<thead>
<tr>
<th>Climate-related despair</th>
<th>Depression</th>
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<tbody>
<tr>
<td>Affect</td>
<td>Empotiness and loss</td>
</tr>
<tr>
<td>Affect responsivenes</td>
<td>Responsive to positive events</td>
</tr>
<tr>
<td>Positive emotions</td>
<td>Present</td>
</tr>
<tr>
<td>Thought content</td>
<td>External (climate-related) problems; diminished future for self and progeny</td>
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<tr>
<td>Self-esteem</td>
<td>Preserved</td>
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</tbody>
</table>

Adapted from DSM-5 distinction of grief from depression. 

To see additional articles in our Climate Change series go to: www.psychiatrictimes.com/climate-change.
Pain Management

THE QUIZ/Chronic Pain and Traumatic Brain Injuries

TRISTAN WRIGHT/FREEMANCreative Commons

TBI sufferers with PTSD also appear to be more likely to have chronic pain.
A. True B. False

The mechanisms for chronic pain following TBI have been identified.
A. True B. False

Which of the following may be possible explanations for post-TBI pain?
A. Disruption in dopamine signaling due to injury to the dopaminergic centers in the brain
B. An inflammatory process involving the nervous system
C. Damage to neurons
D. Alterations in immune function
E. All of the above

Dr. King is in private practice in Philadelphia.

For answers to this quiz, please see page 23.

Case Report

Cariprazine May Decrease Substance Abuse in Patients With Bipolar I Disorder

Larry O. Sanders, MD, and John J. Miller, MD

Cariprazine (Vraylar) is the most recently approved atypical antipsychotic with indications for the treatment of adults with acute mania/mixed mania in bipolar I disorder and schizophrenia. The atypical antipsychotics are a heterogeneous group of medications that like typical antipsychotics all have antagonistic activity on the dopamine-2 receptors (either through pure antagonism or antagonism/partial agonism). While all atypical antipsychotics share 2 properties, dopamine-2 antagonism and various activities at a wide range of serotonin receptors, each atypical antipsychotic has a unique overall receptor binding profile that provides a variety of diverse benefits and/or adverse effects.

Among the atypical antipsychotics, cariprazine is unique in its high potency as an antagonist/partial agonist at the dopamine-3 receptor. Although other atypical antipsychotics have significant activity at the dopamine-3 receptor, cariprazine is uniquely more potent at antagonizing dopamine-3 than dopamine-2, which it does by a factor of 6 to 8 times. Moreover, and possibly more significant, while structurally it is an extremely potent antagonist at the dopamine-3 receptor, functionally it serves as a partial agonist with approximately 70% intrinsic activity (agonism). While the significance of potent antagonism/partial agonism at the dopamine-3 receptor is not fully understood, it is hypothesized to play a role in motivation, reward and depression.

Substance use disorders are a common comorbidity in individuals with bipolar disorder—DSM-5 reports comorbidities of over 50%. During the course of treatment of several patients with comorbid bipolar I disorder and a substance use disorder (primarily alcohol use disorders, but other substances as well) with cariprazine, it was observed that some patients with longstanding and refractory substance use disorders reported a rapid and dramatic decrease in substance use. Following are 3 case reports from clinical practice. Although based on actual patients, the details have been modified to protect patients’ identities.

Case 1

Tony is a 51-year-old stay at home father with a long history of bipolar I disorder and alcohol use disorder, both well-established before he had children. He is the primary care provider for his two very active children while his wife works at home. He does not drink alcohol while parenting, but as soon as his wife relieves him in the evening, he will consume “9 to 12 beers to settle down.” After Tony posted on a public media site how much he missed cocaine, his wife, under standably concerned about his significant substance use issues, brought him in for an early follow-up appointment.

Tony had failed multiple medica-
Sorting Out the Antidepressant “Withdrawal” Controversy

RONALD W. PIES, MD and DAVID OSSER, MD

Consider the following vignettes and what they might teach us regarding so-called “antidepressant withdrawal.”

CASE VIGNETTE

Mr A is a 40-year-old technician who has a diagnosis of MDD. He has been successfully treated with supportive therapy and 75-mg sertraline daily for the past 9 months. He has been in full remission for the past 6 months and asks his psychiatrist about “getting off the meds.” Since this is Mr A’s first episode of MDD, he and his psychiatrist decide that a cautious trial off the sertraline is reasonable.

The dose is reduced to 50 mg daily for 2 weeks; then 25 mg daily for 2 weeks; then 12.5 mg daily (1/2 of a scored 25-mg tablet) for 2 weeks. The patient is seen twice during this period and monitored carefully for any discomfort. Mr A tolerates the taper well, although he does report some mild nausea, occasional headaches, and hypersensitivity to sound, on 12.5 mg daily. Accordingly, the tapering is extended another 2 weeks (for a total of 8 weeks). The medication is then discontinued without difficulty.

Ms B is a 30-year-old financial manager with a history of three episodes of severe MDD over the past 10 years. She has been stable and doing well on paroxetine (60 mg/d) for the past 3 years, prescribed by her family physician, and is now strongly considering having a child. After discussing the risks of continuing an antidepressant during pregnancy, she and her doctor decide to discontinue the paroxetine. The dose is decreased to 40 mg daily for 2 weeks; then 20 mg daily for 1 week; then discontinued. During the first 2 weeks, the patient complains of occasional mild nausea, occasional abdominal cramping, and mild dizziness. However, Ms B is determined to “push ahead” with the tapering process and the schedule is maintained. On 20 mg daily, the patient reports no new or bothersome symptoms, and the paroxetine is stopped after a week.

Within 3 days, the patient calls her physician and complains of intense anxiety, insomnia, restless legs, diarrhea, dizziness, and what she describes as “brain zaps” (“like an electric shock to my head”). The paroxetine is immediately re-started at 20 mg daily, and the patient’s symptoms abated slowly over the next month.

These two vignettes—based on many patients we have encountered over a combined 70+ years of clinical experience—represent two possible outcomes of discontinuing serotonergic antidepressants (SSRIs and SNRIs). In our experience, the first scenario is far more common, and represents sound medical management of the tapering process. The second scenario is not one we have seen in our practice but is commonly reported among the “layperson withdrawal community.” Anecdotal reports of the second type—some with much worse outcomes—have led to extreme claims in the lay media that SSRIs and SNRIs are addictive, and ought to be grouped with known drugs of abuse.1 One website run by a psychiatrist (who will not prescribe antidepressants) declares that these medications “…are habit forming, so withdrawal can be excruciating.”2

While we do not deny that severe reactions can and do occur when antidepressants are stopped suddenly (or the dose reduced too rapidly), we also believe that fears of such “excruciating” experiences are greatly overstated, in the context of proper psychiatric care. At the same time, we acknowledge that many “prescribers” of antidepressants—nearly 80% of whom are primary care physicians—discontinue antidepressants much too rapidly.3 Moreover, as critics of these drugs rightly point out, it is very hard to find detailed, professionally approved guidelines for tapering and discontinuation of antidepressants.4

What do we know about antidepressant withdrawal syndromes?

Among the most thorough recent reviews of antidepressant discontinuation is that of Jha and colleagues,5 who comprehensively analyzed 18 clinical trials of SSRI discontinuation. (Note that these authors consistently use the term “discontinuation symptoms” rather than “withdrawal symptoms”—a point of great contention within the “layperson withdrawal community”6 but consistent with DSM-5, which describes “Antidepressant Discontinuation Syndrome” in terms quite similar to those of Jha and colleagues.) We would summarize the main conclusions of Jha and colleagues as follows:

1 SSRI discontinuation can lead to a wide variety of systemic and neuropsychiatric manifestations, including but not limited to flu-like symptoms; cardiovascular, gastrointestinal, and musculoskeletal complaints; worsening of mood, exacerbation of anxiety, perceptual abnormalities; and insomnia/nightmares.

2 SSRI discontinuation typically has its onset 1 to 10 days after drug discontinuation, and typically resolves spontaneously within 2 to 3 weeks. However, some reports document persistence of SSRI discontinuation (“withdrawal”) symptoms for up to 1 year.

3 The actual incidence of SSRI discontinuation symptoms is difficult to ascertain, because they are not systematically assessed in clinical practice; however, Fava and colleagues6 found that up to 40% of patients reported new-onset of untoward symptoms after abrupt discontinuation of SSRIs (note the key term: abrupt).

4 For more than 60% of patients, SSRI discontinuation will not be associated with any significant symptoms. When present, symptoms range from mild to moderate-to-severe in intensity and, in some cases, may affect multiple organ systems.

5 Paroxetine has a short half-life (approximately 21-24 h), has the highest rates of discontinuation symptoms, compared with other SSRIs.7 Paroxetine is also moderately anticholinergic; has no active metabolites; and undergoes non-linear pharmacokinetics, all of which may contribute to its propensity for discontinuation/withdrawal effects. Fluoxetine has a long half-life and probably has the lowest rates. Although not reviewed by Jha and colleagues, the short half-life SNRI, venlafaxine, is also frequently implicated in discontinuation syndromes, apparently more so than other SNRIs.8

6 The differential diagnosis of apparent SSRI discontinuation/withdrawal symptoms includes various medical conditions; discontinuation of other psychotropic medications; and, importantly, re-emergence of the initial depressive episode. Other research suggests that gradual tapering of the antidepressant does not seem to lower relapse rates, and patients with three or more prior episodes or a chronic course have a much higher relapse risk, after discontinuation of antidepressants.9

7 The pathophysiology of SSRI discontinuation/withdrawal is not completely understood, but probably involves (among other mechanisms) reduced levels of serotonin in the CNS.

8 SSRI discontinuation/withdrawal can usually be resolved within 2 to 3 days by re-institution of the discontinued agent, or introduction of another SSRI. Substituting fluoxetine as a long-acting “buffering” agent is often recommended.

9 Antidepressants may need to be taken for at least 4 to 6 weeks, before the development of SSRI discontinuation/withdrawal becomes a serious concern. There is a general consensus that the longer the patient has taken an SSRI, the more likely or more serious the syndrome, following abrupt discontinuation.

10 SSRI discontinuation/withdrawal can be managed via prevention and treatment strategies, including educating patients regarding risk of discontinuation, using gradual discontinuation, and by resumption of an SSRI for burdensome symptoms.

Dissenting voices

Fava and colleagues disagree with the “mainstream” view of Jha and colleagues.

Clinicians are familiar with the withdrawal phenomena that may occur from alcohol, benzodiazepines, barbiturates, opiods, and stimulants. The results of this review indicate that they need to add SSRI to the list of drugs potentially inducing withdrawal phenomena. The term “discontinuation syn-
First of all, there is no conclusive evidence showing that the pathophysiological mechanisms underlying SSRI/SNRI withdrawal symptoms are similar to those in, for example, alcohol, opioid, barbiturate, or benzodiazepine withdrawal. In addition, the usual hallmarksof “addictive” drugs—such as craving for the drug, compulsive use, intentional overdose, “getting high,” diversion for illicit use, etc—are not characteristic of SSRI/SNRI antidepressants as a class.

Furthermore, the claim by some groups that antidepressants are associated with the development of tolerance requires context and clarification. Unlike genuine substances of abuse, such as alcohol or barbiturates, true tolerance is not commonly observed with antidepressants. The related phenomenon of tachyphylaxis—defined as a loss of previously effective antidepressant treatment response despite staying on the same drug and dosage—is observed in only about 25% of unipolar depressed patients. Results from a study by Zimmerman and colleagues show that the great majority of relapses attributed to so-called “poop out” of the antidepressant are actually due to the initial response having been a placebo response. Viewed clinically, there are important, substantial differences between SSRI/SNRI withdrawal symptoms and the syndromes that follow abrupt discontinuation of drugs of abuse. For example, the mortality rate among patients exhibiting delirium tremens during withdrawal from alcohol is 5% to 25%. Barbiturate withdrawal may be accompanied by seizures in up to 75% of subjects, and about 66% may develop a delirium lasting several days. In this context, delirium-related agitation and hyperthermia can lead to exhaustion, cardiovascular collapse, and death.

Potentially lethal withdrawal reactions appear to be exceedingly rare, or non-existent, when SSRI/SNRI antidepressants prescribed in therapeutic doses are abruptly stopped and are virtually unheard of when these antidepressants are tapered gradually. Indeed, we are unaware of any reports of lethal withdrawal reactions when SSRIs/SNRIs are rapidly or even suddenly discontinued. Similarly, seizures following abrupt discontinuation of SSRIs/SNRIs appear to be exceedingly rare, unlike, say, with sudden discontinuation of barbiturates. In fact, we could find only one case report of an SNRI withdrawal-related seizure, in the context of severe hypokalemia due to vomiting.

The need for a longer tapering period

The vast majority of serious withdrawal symptoms following discontinuation of SSRIs/SNRIs occur when the tapering period is less than 1 to 2 months. This may be particularly the case when the patient has taken the medication for a case or longer. Based on our extensive experience with antidepressants, we believe that serious withdrawal symptoms are extremely rare when tapering periods of 2 to 6 months are used. However, we acknowledge that such long tapering periods are probably uncommon in general medical practice, and even in most psychiatric settings. Indeed, our second vignette, involving a rapid, 3-week taper of high-dose (60 mg/d) paroxetine, is an illustration of poor medical management that may be common in some practice settings. A much slower tapering rate would have been appropriate in the case of Ms B.

In contrast, the first vignette illustrates how judicious and extended tapering of SSRIs/SNRIs (over 8 weeks and longer) can avoid serious withdrawal syndromes. Factors associated with higher risk of serious reactions are shown in the Table.

The vulnerability of the period of antidepressant tapering.

When well-managed, discontinuation of antidepressants need pose a significant clinical problem and should not discourage depressed patients from using these beneficial medications.

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Cariprazine

Continued from page 10

tion trials (including risperidone, paliperidone, aripiprazole, bupropion SR, carbamazepine, lamotrigine, and lithium) for treatment of bipolar I disorder symptoms, so a trial of the novel drug cariprazine was begun as monotherapy. At the next visit the transformation in his appearance and presentation was remarkable. Tony routinely appeared for his appointments quite dishueved. Now, Tony was well-groomed and appeared well rested. He reported that not only was his mood stable, but that he had no urge to drink excessively or use drugs. Over the course of the next 12 months, Tony reduced his consumption of alcohol to “3 beers per night” and he stopped using illicit drugs. His alcohol use continued to decline, and as of the time of this writing he has been abstinent for the past 5 months.

CASE 2

Nora is a 20-year-old self-described “hot mess.” She has bipolar I disorder and ADHD as well as alcohol and cannabis use disorders. She failed out of college and was kicked out of her family home. Upon presentation for her first office visit accompanied by her mother, she was restless, had poor eye contact, and had difficulty communicating a coherent history. When her mother attempted to clarify the history, Nora yelled at her and became very agitated. Several medications, including aripiprazole, were tried to target her symptoms of depression, irritability, restlessness, and poor eye contact. After several months of sub-acute trials (includingrisperidone, paliperidone, aripiprazole, bupropion SR, carbamazepine, lamotrigine, and lithium) for treatment of bipolar I disorder symptoms, so a trial of the novel drug cariprazine was begun as monotherapy. At the next visit the transformation in his appearance and presentation was remarkable. Tony routinely appeared for his appointments quite dishueved. Now, Tony was well-groomed and appeared well rested. He reported that not only was his mood stable, but that he had no urge to drink excessively or use drugs. Over the course of the next 12 months, Tony reduced his consumption of alcohol to “3 beers per night” and he stopped using illicit drugs. His alcohol use continued to decline, and as of the time of this writing he has been abstinent for the past 5 months.

Findings from animal models indicate that cariprazine improves cognition, increases pro-social behavior, and decreases the rewarding effect of cocaine.

He ultimately married, and although he and his wife own and run their own business, he was functionally disabled by his comorbid bipolar I disorder and alcohol use disorder. At the time of his initial presentation he was taking quetiapine, lithium, lamotrigine, bupropion, duloxetine, omega-3 fatty acids, and gabapentin. Subsequent medication trials included various combinations of lurasidone, olanzapine, methylphenidate, and aripiprazole, which provided some benefit for his depression, but his excessive alcohol use persisted.

After adding cariprazine to his medication regimen he reported a dramatic decline in his craving for alcohol, ultimately limiting his alcohol use to 1 or 2 drinks on holidays or special occasions. Subsequently, he was tapered off his previous medications and achieved stability on cariprazine and quetiapine. Matt continues on these two drugs and has now been stable and functioning well for 18 months. His wife stated, “You have not given him his life back, because he never had one. You have given him a life.”

Discussion

These three cases suggest that adding cariprazine to the medication regimen of individuals with comorbid bipolar I disorder and a substance use disorder may improve symptoms of both disorders. Notably, these three individuals reported an abrupt decrease in substance craving and use, which accompanied their improvements in mood symptoms. In our conversations with other psychiatric providers, similar outcomes have been observed.

Bipolar I disorder affects approximately 1% of the general population, and is complicated by substance use disorders. The substance abuse commonly is initially an attempt to self-medicate mood symptoms. After chronic use, substance craving/dependence/withdrawal become additional primary symptoms, further complicating treatment. Ep- receptor antagonism with accompanying intrinsic activity (partial agonism) of approximately 70% may contribute to the decreased craving of substances in patients on cariprazine while simultaneously improving their mood and cognition. However, more research is needed to investigate this possibility.

Randomized, double-blind, placebo-controlled studies are needed before clinicians can confidently prescribe cariprazine for comorbid bipolar I disorder and a substance use disorder. In the three cases presented, cariprazine was prescribed as monotherapy in one case, and in combination with other psychotropic medications in the other two cases.

Caution should always be applied when adding a new medication to an existing regimen, as the possibility always exists of synergistic adverse effects, oppositional pharmacodynamics, drug-drug interactions, and unpredictable unintended outcomes. Treatment should ideally also include structured substance abuse therapy and participation in a 12-step program.

Dr. Sanders is Owner and Medical Director of Sanders-Sclar Psychiatry and Sanders Psychiatry, Littleton, CO; Dr. Miller is Medical Director, Brain Health, and Staff Psychiatrist, Seacoast Mental Health Center, Exeter, NH.

Dr. Miller reports that he is on the Speakers’ Bureau for Sunovion, Otsuka/Lundbeck, Allergan, Teva, and Neurocrine; he is also on the Advisory Boards of Janssen and Alkermes. Dr. Sanders reports that he is a Consultant for Allergan, Takeda, Luxebank, and Sunovion.

References

A global health crisis is emerging because of the changing demographics and care of older adults with schizophrenia. Individuals aged 55 years and older will soon account for 25% or more of the total population of patients with schizophrenia worldwide. Among persons aged 60 years and older with mental and substance-use disorders, schizophrenia ranks third in causes of disability-adjusted life-years. Older adults with schizophrenia also have a substantial impact on health care costs, with an estimated greater expenditure per person compared with most other medical and psychiatric disorders.

Research on older patients with schizophrenia has been neglected; roughly 1% of the schizophrenia literature focuses on this population. With the prevalence of schizophrenia in older adults set to double and reach 1.1 million people in the US by 2025 and 10 million worldwide by 2050, greater attention to research and policy regarding this population is needed.

Morbidity and mortality

Older patients with schizophrenia include individuals with an early-onset that persists into later life and those with a late onset of this condition. There are currently two generations of older adults with schizophrenia: the “old-old” (those 75 years and older) and “young-old” (aged 55 to 74 years). Although more adults with schizophrenia are living longer, their life expectancy is still shorter than that of unaffected individuals. The risk of mortality is two to three times greater in patients with schizophrenia than in the general population, and this gap has been increasing over the past decades. In older adults with schizophrenia, the mortality rate and deaths caused by suicide and accidents are higher than in healthy peers.

Positive and negative symptoms

It has been commonly understood that positive symptoms of schizophrenia decline in later life, while negative symptoms dominate the presentation in older age. However, findings from several studies have invalidated this notion. The International Study of Schizophrenia (ISoS) assessed 18 global cohorts over 15- and 25-year periods and found 77% of patients had no evidence of significant negative symptoms over the course of their illness. Similarly, a longitudinal study of institutionalized geriatric patients with schizophrenia showed no significant changes in negative symptoms over time. From a clinical perspective, negative symptoms do not dominate in older adults with schizophrenia and are often expressed in a similar magnitude seen in younger patients.

Cognition

Cognitive deficits are a fundamental feature of schizophrenia; they are observed across the life span of affected individuals and are among the strongest predictors of functional disability. Functional disability accounts for roughly half of schizophrenia treatment costs, which increase substantially later in life. Older adults with schizophrenia have significant cognitive deficits in executive functioning, speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning, and problem-solving.
Research has shown a heterogeneity in the trajectory of cognitive function in older patients with schizophrenia based on residential status. Cognitive decline in community-dwelling patients with schizophrenia is similar to that in unaffected individuals until the age of 65 to 70 years. After 70 years of age, an accelerated cognitive decline in older adults with schizophrenia cannot be ruled out. Cognitive decline is also greater in older adults with schizophrenia who had long periods of institutionalization, especially those over 65 years of age.

In a longitudinal study, three cognitive function trajectories in patients with schizophrenia were identified. They included stable cognition observed in 50% of the cohort, a slow decline in 40%, and a rapid decline in 10%. The course of cognitive decline for healthy peers is similar to the stable schizophrenia group.

Because most studies found no significant decline in cognitive function in older patients with schizophrenia compared with their healthy peers, it is believed that schizophrenia is a syndrome of premature aging. Preserving and improving cognitive function in older adults with schizophrenia are thus important objectives with significant individual and public health benefits.

Dementia
Differentiating between schizophrenia and Alzheimer disease with psychosis in older adults can be difficult, but there are distinguishing features (Table 1). The prevalence of dementia in older adults with schizophrenia is expected to increase significantly. Older individuals with schizophrenia have a two-fold increased risk of developing dementia before the age of 80 years when compared with the general population. Several factors associated with the increased risk of dementia include age, low educational attainment, premorbid cognitive dysfunction, cardiovascular disease, polypharmacy, and a history of alcohol and/or substance abuse.

The etiology of dementia in older adults with schizophrenia remains unknown. However, long-term exposure to a high anticholinergic burden is associated with cognitive deficits in individuals with and without schizophrenia. It is interesting to note that older adults with schizophrenia and a high anticholinergic burden have a cognitive impairment profile consistent with that observed in Alzheimer dementia.

The Anticholinergic Cognitive Burden scale is a useful tool to identify patients at risk for anticholinergic-related cognitive impairment. In older adults with schizophrenia, the anticholinergic burden should be assessed before additional medication is prescribed.

Insight
A common feature in schizophrenia is impaired insight—more than 50% of individuals have moderate to severe deficits. Impaired insight significantly affects health outcomes by reducing patients' awareness of their mental disorder, its symptoms and implications, and treatment adherence. In a review that examined the effects of aging on insight into illness in adults with schizophrenia, impaired insight followed a U-shaped trajectory. More specifically, insight is severely impaired during the first episode of psychosis, modestly improves during midlife, and declines again in later life. The association between impaired insight and illness severity, as well as cognition, is stronger in older adults with schizophrenia than in younger patients. Noninvasive neurostimulation techniques, cognitive-enhancing medications, and early intervention to improve insight into illness should be considered for older individuals with schizophrenia.

Pharmacotherapy
Older adults are more susceptible than younger individuals to the adverse effects of antipsychotics. This is because of age-related pharmacokinetic changes that increase the distribution volume and elimination half-life of antipsychotic drugs, changes in the permeability of the blood-brain barrier that increase drug availability in the brain, and pharmacodynamic changes that decrease the absolute number of dopaminergic neurons and D2 receptor density in the brain. In older adults with schizophrenia, extrapyramidal symptoms occur at lower D2 receptor occupancies than in younger patients. Older age is also a risk factor for antipsychotic adverse effects such as parkinsonism, tardive dyskinesia, falls, and metabolic syndrome. These drug effects can further impair cognitive and functional capacity in older patients with schizophrenia.

Despite the limited research and challenges in using antipsychotics to treat older adults with schizophrenia, these drugs are effective in controlling psychotic symptoms. Olanzapine and risperidone are efficacious in treating older patients with non-resistant schizophrenia. We recommend risperidone as the first-line treatment in this population because olanzapine has a high anticholinergic burden. Other second-generation antipsychotics with a low anticholinergic burden should also be considered, such as aripiprazole and ziprasidone.

Because of the risk of agranulocytosis, few studies have examined the efficacy of clozapine in older patients with treatment-resistant schizophrenia. Nevertheless, we believe it is worth considering over other antipsychotic medications that have an equally high anticholinergic burden, such as olanzapine.

In view of their adverse effects, antipsychotic drugs should be prescribed with care and at the lowest therapeutic dose. Table 2 lists antipsychotic dosing regimens for older adults with schizophrenia. A helpful method to determine the appropriate dosage and minimize adverse effects is to measure a patient's serum prolactin levels.

A longitudinal positron emission tomography study found the antipsychotic dosage can be successfully reduced in over 80% of patients with stable late-life schizophrenia. Moreover, a lower dosage led to fewer adverse effects and extrapyramidal symptoms, less hyperprolactinemia, and improved clinical symptoms through reduced D2 receptor occupancy.

A follow-up study found that reducing antipsychotic dosages by up to 40% increased D2 receptor availability in the striatum. This increase allows the striatum D2 receptors to contribute more significantly to cognitive function, and it can be targeted by interventions that promote cognitive enhancement in late-life schizophrenia.

The decision to start a second-generation antipsychotic in an elderly patient with dementia is not to be taken lightly. In April 2005, the FDA asked manufacturers of second-generation antipsychotics to include a “black box” warning in their label. Using clinical data, the FDA determined that elderly patients with dementia who were treated with second-generation antipsychotics for behavioral disorders had an increased risk of mortality. In June 2008, the FDA extended this warning to include first-generation antipsychotics.

Nonpharmacologic psychosocial interventions
Nonpharmacologic interventions help reduce psychotic symptoms and augment pharmacotherapy. Cognitive remediation is a behavioral intervention developed to improve cognitive deficits by repeated task practice and/or strategy acquisition. Although patients with early-stage and early-chronic schizophrenia have greater improvement in their working memory than controls, the long-term benefits of these interventions are not well established.

Table 1. Characteristics of Alzheimer disease with psychosis compared with those of schizophrenia in older adults

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Alzheimer disease</th>
<th>Schizophrenia</th>
</tr>
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<tbody>
<tr>
<td>Delusions</td>
<td>Persecutory, theft, and infidelity</td>
<td>Persecutory and thought control</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>Visual more common</td>
<td>Auditory more common</td>
</tr>
<tr>
<td>Presentation</td>
<td>Flattened affect, avolition, apathy, poverty of speech and thought</td>
<td>Disengagement and apathy</td>
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<td>Family history</td>
<td>Alzheimer disease</td>
<td>Major mental illness</td>
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<tr>
<td>Trajectory</td>
<td>Progressive decline with aging</td>
<td>Fluctuates</td>
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SCHIZOPHRENIA: PART 2
TABLE 2. Common antipsychotic dosing regimens and black box warnings for older adults with schizophrenia*13,16

<table>
<thead>
<tr>
<th>Medication</th>
<th>Initial dose (mg)</th>
<th>Titration (mg)</th>
<th>TMD (mg)</th>
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<td><strong>Second-generation antipsychotics</strong></td>
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<tr>
<td>Aripiprazole</td>
<td>2 to 5</td>
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<td>10 to 15</td>
<td>75</td>
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<td>Clozapine</td>
<td>6.24 to 12.5</td>
<td>12.5 to 25</td>
<td>100 to 200</td>
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<td>Paliperidone</td>
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<tr>
<td>Quetiapine</td>
<td>12.5 to 50.0</td>
<td>25 to 50</td>
<td>100 to 450</td>
<td>6</td>
</tr>
<tr>
<td>Risperidone</td>
<td>0.25 to 0.5</td>
<td>0.25 to 0.5</td>
<td>1 to 4</td>
<td>3 to 20</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>20</td>
<td>20 to 40</td>
<td>20 to 80</td>
<td>7</td>
</tr>
<tr>
<td><strong>First-generation antipsychotics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td>0.25 to 0.5</td>
<td>0.25 to 0.5</td>
<td>0.25 to 2.0</td>
<td>12 to 22</td>
</tr>
</tbody>
</table>

TMD, target maintenance dose. Note: All of the listed antipsychotics carry an FDA black box warning increased risk of mortality for older adults with dementia.

memory after receiving cognitive re-mediation than older patients, adaptations in existing programs can address the cognitive needs of older individuals.

Cognitive-behavioral therapy is another nonpharmacologic intervention widely used to resolve problems with social relatedness, positive and negative symptoms, and mood in older adults with schizophrenia. Social skills training has also been used in this population to treat difficulties with social interaction, while exercise programs help reduce declines in cognition and activities of daily living. The use of mobile devices to facilitate these psychosocial interventions can improve the dissemination of psychosocial interventions in the community setting.

Neurostimulation

Given the adverse effects of antipsychotic drugs in older adults with schizophrenia, alternative treatments are needed. Brain stimulation in the form of electroconvulsive therapy, transcranial magnetic stimulation, and deep brain stimulation offer viable solutions, especially in the context of medication resistance. Bilateral electroconvulsive therapy has been effective for both acute and maintenance treatment of older adults with early-onset schizophrenia, but not for older patients with late-onset schizophrenia. A pilot study of magnetic seizure therapy in patients with treatment-resistant schizophrenia showed significant clinical and quality-of-life improvement, but more trials with larger cohorts are needed. Unfortunately, transcranial magnetic stimulation and deep brain stimulation have not been evaluated in older adults with schizophrenia.

Conclusion

The current knowledge of schizophrenia in older adults reveals a different state of health compared with younger affected individuals. More research to understand the neurology underlying its clinical features, along with the development of novel age-appropriate services and treatments to improve impairments in older adults with schizophrenia, should be prioritized.

Dr Khan is Research Fellow, Centre for Addiction and Mental Health (CAMH), and Campbell Family Research Institute, and Department of Psychiatry, University of Toronto, Ontario, Canada; Dr Rajji is Deputy Physician-in-Chief, Clinical Research, and Chief, Adult Neurodevelopment and Geriatric Psychiatry, CAMH, and Campbell Family Research Institute. He is also Canada Research Chair, Neurostimulation for Cognitive Disorders, and Associate Professor of Psychiatry, University of Toronto.

The authors report no conflicts of interest concerning the subject matter of this article.

References


Cognitive Training for Neural System Dysfunction in Psychotic Disorders

Sophia Vinogradov, MD

Over the last decade or so, our field has experienced a radical shift in our understanding of schizophrenia and other serious psychotic disorders, such as schizophrenia and bipolar disorder with psychosis. We now understand that these are neurocognitive disorders (i.e., how neural systems in the brain represent and process information). We also understand that they are neurodevelopmental disorders with genetic components and antecedents during gestation. The developmental course unfolds with increasing signs, symptoms, and cognitive dysfunction, until the onset of the first episode of psychosis during adolescence or early adulthood. Cognitive deficits are more significant determinants of functional outcome than are symptoms, although current psychiatric treatments focus on (or mostly) on symptom management.

Accumulating evidence indicates that psychotic disorders constitute syndromes rather than diseases per se. Groups of patients can show a common clinical phenotype with multiple different etio-pathogenic factors that contribute to illness onset and expression. Patients with different clinical diagnostic phenotypes (such as schizophrenia rather than bipolar disorder with psychosis) can show similar underlying patterns of cognitive dysfunction and neurobiological abnormalities. New insights into the pathogenesis of psychotic disorders has spurred research focused on key domains of neural system dysfunction and how brain plasticity mechanisms can be harnessed to drive healthier neural sys-
tem functioning, improve cognition, and support functional recovery.

**Cognitive and neural system dysfunction in psychotic disorders**

Although the clinical symptoms of psychotic disorders are dramatic and are what most clinicians focus on as their treatment targets, impairments in a wide range of cognitive function are observed in these illnesses, ranging from the earliest stages of information processing in the brain, to higher-level abilities to abstract, to read social cues, to self-reflect, and to engage in meta-cognition. These various areas of cognitive dysfunction are accompanied by abnormalities in their neural system correlates. Moreover, patients exhibit a fair amount of cognitive and neural system heterogeneity, both within and across traditional diagnostic groupings—different patients will often have different patterns of impairment. Nonetheless, the following general categories of findings are commonly observed:

- **Sensory and perceptual processing abnormalities:** A range of subtle deficiencies in representing and processing auditory and visual information, including socially relevant information, that can show functional consequences.
- **Learning and memory deficits:** Impairments in how the brain encodes, learns, and makes decisions based on new information, including socially relevant information; responds to changes in rewarding or punishing contingencies in the environment; encodes and remembers autobiographical events (episodic memory); and learns associations and meanings (semantic memory).
- **Executive dysfunction (i.e., impaired cognitive control):** Deficits in attention and working memory; problems with inhibitory control; impaired abstraction, reasoning, planning, sequencing.

In psychotic disorders, the emergent picture is one of a brain that has undergone aberrant patterns of neurodevelopment, with reduced functional connectivity among key neural systems and reduced efficiency in its cognitive and socio-affective operations. This suggests that to improve cognition and functioning, it is essential to begin treatment as early as possible in the course of illness. Interventions designed to correct or compensate for abnormal neural system functioning must be started before irreversible maladaptive changes in the cortical and subcortical representational systems have taken root. Cognitive remediation and cognitive training approaches are used to improve cognition and are increas-

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**Key Take Home Points**

- Schizophrenia, schizoaffective disorders, and bipolar disorder with psychosis are disorders of how neural systems in the brain represent and process information (neurocognitive disorders).
- Cognitive dysfunction in these disorders ranges from the earliest stages of auditory and visual information processing in the brain, to higher-level abilities to learn and encode new information, to read social cues, and engage in meta-cognition.
- Cognitive dysfunction is a more significant determinant of functional outcome than are symptoms, although most current psychiatric treatments focus only (or mostly) on symptom management.
- Cognitive remediation and cognitive training explicitly seek to improve cognition by improving brain information processing.
- Research is needed to identify “which specific program?” “at what specific dose?” for “which specific patterns of cognitive dysfunction?” and in “which specific individual?”
- Interested clinicians and consumers can consult PsyberGuide.org, a non-profit organization whose mission is to help consumers choose effective and accessible mobile health technologies, including cognitive training programs.

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Cognitive remediation vs cognitive training

Findings from meta-analyses indicate that a large variety of cognitive remediation protocols result in modest gains in overall cognitive functioning (effect sizes of about 0.4).²⁻⁴ No specific cognitive remediation method has been proved to be most effective.

The term “cognitive remediation” is a good descriptor for an intervention that is often multi-modal, using several approaches simultaneously (Table). It can be conceptualized as a set of rehabilitative psychological treatments aimed at improving aspects of cognitive performance and behavior, which can of course also have effects on brain function and structure.

In contrast, the term “cognitive training” describes an explicitly neuroscience-informed approach to driving neural system plasticity in a well-defined neurocognitive operation or set of operations that may then generalize to other cognitive, behavioral, and functional domains. One of the best-studied examples of this kind of cognitive training utilizes approximately 10 hours of computerized visual speed-of-processing training in older adults. It has been associated with significantly improved cognition, lower rates of depression, and lower medical expenditures up to 10 years after the intervention.³

In our own research, we often go one step further and use the term “targeted cognitive training” when describing cognitive training exercises that are defined in terms of specific neurocognitive target(s). Examples of specific neurocognitive targets include auditory processing abnormalities or social cognitive impairments (eg, eye gaze detection, facial emotion recognition, vocal prosody recognition). This approach is best conceptualized as a neurobiological treatment aimed at driving brain changes in neural systems that will generalize to improvements in cognitive performance and behavior (Table). It can be delivered alone or as part of a larger treatment package.

### Cognitive Remediation Programs

- Neuropsychological rehabilitation approach often focused on remediation of a wide array of deficits; rooted in several decades of cognitive psychology and neuropsychology research; sometimes referred to as a “top-down” approach

- Often viewed as a psychological treatment that can also generate neural system change; research has been dominated by a treatment development paradigm

- Multiple active ingredients often embedded together in real-world settings to maximize behavioral change; eg, programs often use explicit instruction on transfer of skills to real-world situations, group skills training and support, compensatory behavioral strategies, etc

### Targeted Cognitive Training Approaches

- Focused on inducing neuroplasticity in specific distributed neural systems; based on integrative neuroscience research; sometimes (inaccurately) referred to as a bottom-up approach

- Viewed primarily as a “neurological” treatment that drives neural system change and thus behavior change; research has been dominated by a mechanistic experimental medicine paradigm

- Specific drivers of cognitive change are targeted, based on hypotheses about underlying pathophysiology; mechanisms and biomarkers of response to intervention are identified

- Training makes use of computerized exercises that are individually tailored to drive learners to their threshold at a high-rewarded schedule; exercises focus intensively, in a targeted manner, on relevant component cognitive and social cognitive operations, concomitant with domain-specific attention and working-memory operations

- Training has generally aimed to be delivered at a rate of 4-5 sessions per week for a total of 20-40 h in a given cognitive domain; however, less intensive regimens of training have been studied as well

### Treatment Delivery

- Treatment may (but does not always) include computerized exercises providing graduated repetitive practice across a wide range of higher-order cognitive domains, usually using the visual modality

- Training often delivered at a rate of 2-3 sessions per week for a total of approximately 20-30 h; however, both lower and higher numbers of sessions over different time spans have been studied

### Examples of Software Programs

- Examples of available software programs that have been studied as part of cognitive remediation programs include Cogpack, CogRehab, RehaCom, Happy Neuron, and a range of educational software

- Examples of available software programs that have been studied in cognitive training research include Happy Neuron and Brain HQ (Posit Science) exercises

<table>
<thead>
<tr>
<th>TABLE. Proposed conceptualization of cognitive remediation vs targeted cognitive training</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cognitive Remediation Programs</strong></td>
</tr>
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</tr>
</tbody>
</table>

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A targeted cognitive training approach

The effects of mobile targeted cognitive training of auditory processing (TCT) versus control condition computer games (CG) were studied in a double-blind randomized trial.¹¹ The study comprised 147 young adults with recent-onset schizophrenia (average age of 21 years) treated in two university-based first-episode clinics. Participants received laptop computers and instructions to complete 40 hours of training or the control condition games over approximately 8 weeks, performed on their own schedule at home. Check-ins and support were provided by the researchers.

The CET group had greater gray matter preservation in the left hippocampus, the parahippocampal gyrus, and the fusiform gyrus as well as gray matter increases in the left amygdala. These findings were related to improved cognition.¹¹ The EST group also had improved resting-state and task-related functional connectivity in the prefrontal cortical regions; these findings were also associated with improved cognition.²⁻¹⁰

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²⁻⁴

Eack and colleagues⁶ studied cognitive enhancement therapy (CET) vs enriched supportive therapy (EST) in 58 young individuals with prodromal schizophrenia; their average age was 26 years. CET combined 60 hours of computerized cognitive exercises using CogRehab software over 2 years in a specialized outpatient setting in conjunction with 45 sessions (90 minutes each) of social skills group exercises.

After 1 year of treatment, improvements on cognitive measures were not observed in CET participants compared with EST. After 2 years, moderate cognitive improvement was observable. Gains on measures of social cognition, cognitive style, social adjustment and symptoms were evident. At 1-year follow-up, gains on social and symptom measures were maintained and cognitive gains made during active training were significantly associated with improvement in functional outcome.⁷

It is interesting to note that cortical surface area and gray matter volume at baseline, especially in temporal cortex, moderated the effects of CET on social cognitive outcomes. Compared with the EST group, the CET group showed increased gray matter volumes and cortical thickness. Combined with an enriched supportive therapy (EST) approach, the CET group showed increased gray matter volumes and cortical thickness. Combined with an enriched supportive therapy (EST) approach, the CET group showed increased gray matter volumes and cortical thickness.
Using Pharmacogenetics in Making Treatment Decisions for Schizophrenia

Daniel J. Müller, MD, PhD
Kazunari Yoshida, MD, PhD

The term “pharmacogenetics (PGx)” was first coined in 1959 with the aim of identifying clinically meaningful genetic predictors of responses to drug treatments and their adverse effects. PGx addresses the limitations of the traditional non-biomarker based “trial-and-error” procedure in selecting psychotropic drugs for patients with psychiatric disorders, including schizophrenia. A combination of pharmacokinetics and pharmacodynamics underlie interindividual differences in drug responses and adverse effects; therefore, PGx focuses on genetic variants involved in pharmacokinetics and pharmacodynamics (Table).

Numerous genetic variants associated with antipsychotic responses and adverse effects in the treatment of schizophrenia have been identified. Based on such genetic information, specific recommendations for treatment with psychotropic drugs, including antipsychotics, have been proposed for clinical practice.

Clinical availability of PGx information

Most antipsychotics are metabolized by cytochrome P450 (CYP) enzymes, (primarily CYP1A2, CYP2D6, and CYP3A4), while other CYP enzymes such as CYP3A5 and CYP2C19 are involved in the metabolism of only a few antipsychotics. The genes encoding these CYP enzymes are polymorphic, resulting in interindividual differences in antipsychotic metabolic abilities.

Four classes of CYP metabolizer profiles have been established according to the multiallelic nature of the CYP enzyme genetic construct: poor, intermediate, normal (extensive), and ultra-rapid metabolizers. Most of the currently available clinical recommendations are based on gene variants that affect CYP enzyme activity.

Based on the CYP2D6 phenotype, the FDA provides information on PGx biomarkers in the drug labeling for nine antipsychotics (aripiprazole, aripiprazole lauroxil, brexpiprazole, clozapine, iloperidone, perphenazine, pimozide, risperidone, and thioridazine). For seven of these nine antipsychotics (aripiprazole, aripiprazole lauroxil, brexpiprazole, clozapine, iloperidone, pimozide, and thioridazine), dosing adjustment recommendations are provided for individuals identified as CYP2D6 poor metabolizers. For example, it is recommended to administer half of the usual dose of aripiprazole to patients who are known to be CYP2D6 poor metabolizers because at standard doses the risk of adverse effects is increased with higher drug plasma levels.

The Pharmacogenomics Knowledgebase (PharmGKB), an NIH-funded resource, provides clinically relevant PGx information, including dosing guidelines and drug labels. In addition, drug labels or expert recommendations provided by several resources are summarized on the PharmGKB website (www.pharmgkb.org).

Using these resources, Bousman and colleagues summarized the current gene-drug interaction information and proposed a minimum testing panel that can serve as a primer for clinical implementation. A total of 448 gene-drug interactions were identified in psychiatry: only 31% (7%) of them satisfied the criteria for the highest level of evidence from PharmGKB (level 1A or 1B), drug labels (testing recommended or required), and clinical guidelines (Clinical Pharmacogenetics Implementation Consortium [CPIC] or Royal Dutch Association for the Advancement of Pharmacy–Pharmacogenetics Working Group [DPWG]). Among those, with the highest level of evidence, 59% involved the CYP2D6/CYP2C19 genes and antidepressant medications (eg, SSRIs and tricyclic antidepressants).

Several gene–drug interactions with high-level evidence were identified between 2 human leukocyte antigen genes (HLA-A and HLA-B) and three anticonvulsants and/or mood stabilizers (carbamazepine, oxcarbazepine, and phenytoin). High-level evidence interactions involving the CYP2C9 and PGLO genes were reported to phenytoin and valproic acid, respectively. Regarding antipsychotics, the following five gene–drug interactions satisfied the criteria for the highest level of evidence: CYP2D6 and aripiprazole, haloperidol, pimozide, risperidone, and zuclopenthixol.

Based on the gene–drug interaction evidence, a minimum PGx testing panel for psychiatry was proposed, in which 16 variant alleles within the CYP2C9, CYP2C19, CYP2D6, HLA-A, and HLA-B genes were included.

This proposed panel is clinically relevant; however, readers should consider certain limitations, including:

1. The proposed panel does not address gene–gene interactions.
2. The proposed minimum panel requires regular updates in line with PGx resource updates (eg, CPIC).
3. PGx testing should be used as a support tool, along with other information (eg, age, sex, ethnicity, and concomitant medications), and should be applied in line with other clinical treatment guidelines. While recommendations exist on how to use pharmacokinetics variants for some antipsychotics, no pharmacodynamics gene variants for antipsychotics have been proposed for clinical practice to date.

A number of commercial PGx testing tools including pharmacodynamics gene variants are being offered by several commercial companies for use in clinical practice. A recent survey evaluated physicians’ opinions of PGx testing and their experiences using such tests for prescribing psychotropics through the The Individualized Medicine: Pharmacogenetic Assessment and Clinical Treatment (IMPACT) study. Of the 168 clinicians surveyed, 80% believed that PGx testing will become a common standard in psychiatric drug treatment; moreover, these responders were satisfied or very satisfied with the genetic information provided. These findings indicate the feasibility and suggested clinical utility of PGx testing.

In several studies, including randomized controlled trials, the clinical utility of PGx testing for antidepressants has been investigated. A recent meta-analysis included four randomized controlled trials and two open-label controlled cohort studies. The findings indicate that treatment guided by PGx testing, including combinatorial testing, is superior to treatment as usual in response and/or remission rates in the acute treatment of depression.

However, further investigation focusing on the clinical validity and efficacy of single and combinatorial PGx testing for antipsychotic treatment responses is warranted. Currently, some randomized controlled trials evaluating the clinical utility of PGx testing on antipsychotics in patients with schizophrenia are underway (eg, NCT02573168 and NCT02566037), which should contribute to important advances in this field.

Precautions for implementation of PGx in clinical practice

While PGx testing, is promising in the treatment of schizophrenia, certain limitations should be considered when clinicians rely on PGx tests without knowing their limitations. For example, a clinical case report published in the American Journal of Psychiatry provided a warning regarding the potential warrant of implementation of PGx testing in clinical practice. It described a male patient with treatment-resistant schizophrenia, aged 25 years, who showed rapid improvement following clozapine administration despite the fact that the PGx test used for the patient did not recommend clozapine for his treatment. He was judged to be a poor responder to clozapine based on the assessment of several
### TABLE: Recommendations for CYP2D6 metabolizer status and five antipsychotics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug labels(^{14})</th>
<th>CPIC level(^{15})</th>
<th>PharmGKB(^{14,16})</th>
<th>Dosing guidelines(^{17})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FDA</td>
<td>EMA</td>
<td>HCSC</td>
<td>PMDA</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Actionable PGx</td>
<td>Actionable PGx</td>
<td>Actionable PGx</td>
<td>N/A</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Pimozide</td>
<td>Testing required</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Informative PGx</td>
<td>Informative PGx</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Zuclopenthixol</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Notes: “Testing required” states or implies that some sort of genetic testing should be conducted; actionable PGx does not discuss genetic testing for gene variants, but contains information regarding changes in efficacy, dosage, or toxicity due to such variants; informative PGx mentions gene involvement in the metabolism or pharmacodynamics of the drug, but there is no information to suggest that variation in these genes leads to a different response. CPIC levels are as follows: A, genetic information should be used to change prescribing of affected drug; B, genetic information could be used to change prescribing of the affected drug; C, no prescribing actions are recommended; D, there are few data. The PharmGKB clinical annotation levels of evidence are as follows: level 1A and level 1B = high; level 2A and level 2B = moderate; level 3 = low; level 4 = preliminary. FDA, Food and Drug Administration; EMA, European Medicines Agency; HCSC, Health Canada (Santé Canada); PMDA, Pharmaceuticals and Medical Devices Agency, Japan; PGx, pharmacogenetics; N/A, not applicable; PM, poor metabolizers; IM, intermediate metabolizers; UM, ultra-rapid metabolizers.

**Findings** indicate that treatment guided by pharmacogenetic testing may be superior to treatment as usual in response and/or remission rates in the acute treatment of depression.

**Conclusion**

In summary, PGx has the potential to optimize antipsychotic treatments and overcome conventional “trial-and-error” approaches. PGx testing has already been implemented in clinical practice. In fact, at least five major US medical centers (St. Jude Children’s Research Hospital, Vanderbilt University Medical Center, University of Florida Health Shands Hospital, Mayo Clinic, and Mount Sinai Medical Center) have implemented PGx testing into clinical care based on available expert consensus recommendations. For the time being, only recommendations for CYP2D6 metabolizer status and several antipsychotics (eg, aripiprazole, haloperidol, pimozide, risperidone, and zuclopenthixol) would meet sufficient evidence-based criteria for clinical utility (Table).

With advancements in the available technology and applied methods, including genome-wide association studies and targeted gene approaches, a number of new gene variants associated with antipsychotic responses and adverse effects have been identified and may be associated with clinical efficacy to predict clinical phenotypes. Additional well-designed randomized controlled trials with large sample sizes of patients from a variety of ethnicity groups, standardized clinical PGx guidelines, and increased genetic variants, including the DRD2, UGT2B15, CYP2C19, CYP2D6, HLA-B15.02, HTR2C, and MTHFR genes.

However, it should be noted that none of these genes reached Level 1A or 1B based on PharmGKB evaluations. Thus, most of the genetic information collected in this case was of limited use regarding prediction of clozapine response while other clinical factors were not considered. Consequently, PGx testing should be seen as a companion decision-support tool, under consideration of all available individual clinical and demographic information available, and not be interpreted as an alternative or substitute to protocol-based care for clinicians in their attempt to optimize pharmacological treatment.

That availability of commercial PGx tests is increasing at a rapid pace. However, it is also important to consider that tests are not standardized for gene and alleles and the interpretation is therefore inconsistent across the available PGx tests. Consistent with this notion, a recent study reported on the level of agreement in pharmacogenetic medication recommendations across four PGx tests (CNS-Dose\(^{6}\), Genecept\(^{6}\), GeneSight\(^{6}\), and Neuropharmagen\(^{6}\)). The agreement was generally modest (eg, antidepressants, 56%; anxiolytics/hypnotics, 56%; antipsychotics, 55%), which indicates that PGx tests are not interchangeable and that standardization across these tests is warranted. Taken together, these findings reflect the need for further standardization of genetic-based phenotyping across PGx tests.

**PGx of antipsychotic treatment response and specific adverse effects**

A number of genetic variants associated with antipsychotic response and adverse effects (eg, tardive dyskinesia, antipsychotic-induced weight gain, and clozapine-induced agranulocytosis) have been found. For example, among several gene variants associated with tardive dyskinesia, the association of the vesicular monoamine transporter 2 (VMAT2) gene with tardive dyskinesia is consistent with recent clinical evidence that showed that a novel selective VMAT2 inhibitor, valbenazine, improved tardive dyskinesia.

Other findings from research that focused on antipsychotic-induced weight suggest consistent results for several genes implicated in appetite/satiety regulation. Our group is currently developing a multi- gene panel to assess individual risk of antipsychotic-induced weight gain, and the preliminary results have been promising. Nevertheless, further research is needed to apply recommendations based on pharmacodynamic variants for antipsychotics to clinical practice. Notably, polygenic risk scores, which represent the total number of risk alleles carried by an individual, weighted by the effect size from the genome-wide association studies, have been suggested to be associated with antipsychotic response in patients with schizophrenia. Several studies and targeted gene approaches, a number of new gene variants associated with antipsychotic responses and adverse effects have been identified and may be associated with clinical efficacy to predict clinical phenotypes.

With advancements in the available technology and applied methods, including genome-wide association studies and targeted gene approaches, a number of new gene variants associated with antipsychotic responses and adverse effects have been identified and may be associated with clinical efficacy to predict clinical phenotypes.

**Conclusion**

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With advancements in the available technology and applied methods, including genome-wide association studies and targeted gene approaches, a number of new gene variants associated with antipsychotic responses and adverse effects have been identified and may be associated with clinical efficacy to predict clinical phenotypes. Additional well-designed randomized controlled trials with large sample sizes of patients from a variety of ethnicity groups, standardized clinical PGx guidelines, and increased...
awareness of the benefit and limitations of PGx will be needed to implement fully in clinical practice.

Dr Yoshida is a Postdoctoral Research Fellow, Centre for Addiction and Mental Health, Toronto, ON, Canada, and a Psychiatrist, Department of Neuropsychiatry, Keio University School of Medicine, Tokyo, Japan; Dr Müller is Head, Pharmacogenetics Research Clinic, Centre for Addiction and Mental Health, and Professor, Department of Psychiatry, University of Toronto, ON.

The authors report no conflicts of interest concerning the subject matter of this article.

References


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-George B., psychologist

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SCHIZOPHRENIA: PART 2

Overheard Conversation, ICU

Richard M. Berlin, MD

-from a Line by Roberto Bolaño

I am dying with many things to say.

Do I have to speak? I know you know

My love was like mist thrown from the waves.

When I die, you will have many things to say.

Once more, my love, I will not obey.

March can be hushed and covered with snow.

I am dying with many things to say.

Do I have to speak? You know what you know.

Dr Berlin is Instructor in Psychiatry, University of Massachusetts Medical School, Worcester, MA.
A Call for Articles

Psychiatric Malpractice
Grand Rounds

With the help of Editor in Chief Emeritus James L. Knoll IV, MD, the editors at *Psychiatric Times* cordially invite you to submit an article about a “what if” legal dilemma for a series of online articles about psychiatry and the law.

The goal of the series is to provide real-world reflections by psychiatrists facing a possible malpractice issue. Dr. Knoll will follow up with reflections, information, and resources, offering context and perspectives to our readers who may be experiencing a similar situation. The follow-up analysis should by no means be considered professional advice.

Please submit your 1200-word manuscript and CV by May 1, 2019, for consideration to editor@psychiatrictimes.com, with “Grand Rounds: Malpractice” in the subject line. Of course, we always need to be careful about confidentiality. If you are submitting a real-life case, all identifiers should be obscured.

Note: This is not a contest and selection will be at the sole discretion of the editors. We cannot promise print publication, but if selected, your article will appear on our website. Only submissions by psychiatrists will be considered.
Calm, Strength, and Happiness

Mindfulness is referred to as “coming home,” a practice that enables one to become grounded and unwavering. Negative distortions are encouraged to be challenged. The importance of learning from positive opportunities that he terms “jewels,” is stressed—no matter how simple, given the potential benefits derived from their accumulation. The relationship between positive and negative experiences is described, as well as the release of bias by the use of positive practices.

Other topics include determination, attachments, unlearning helplessness, gratitude, “altruistic joy,” and the relation of thankfulness to resilience. Liking and wanting are compared and contrasted. Readers are encouraged to find the “sweet spot” and to cultivate the “Inner Nurturer.” Various aspects of intimacy, temperamental differences, and interpersonal relations are explored, including personal autonomy, empathy, forgiveness, and the need to seek and understand our common humanity. The concluding section addresses courage, aspiration, and generosity. Readers are encouraged to seek outlets for gifts and talents, know what one wants from life, and to honor this with a growth mindset.

Dr Khajuria is a Practicing Psychiatrist and Adjunct Faculty, Wright Institute, Berkeley, CA.

References
The Movie

Continued from page 2

By ALAN M. BLEU, M.D.

The English Patient

Case in point: a woman with ruinous self-esteem was devastated when would-be connoisseur at a Gotham dinner party savaged her because she found The English Patient a terminal bore. Wasn’t she aware that the best critics, as well as Manhattan at large, were certain it was Oscar-bound?

She was comforted when I said that I, too, thought the picture a bloated bore. My agreement strengthened a dawning recognition spurred by our work that she wasn’t a socially inept utter boob—her rancorous husband’s default perception. (Of course, I defend to the death your right to admire The English Patient. Even professional film criticism may rationalize private taste into the public area.)

Patients in therapy frequently worry that speaking about a film they hate won’t ruin it for me. I emphasize they needn’t be concerned. Knowing in advance that Russell Crowe’s gladiator or the semi-toasted English Patient expires before the boat-office. If clinical accuracy has to be sacrificed for moving the plot along, so be it.

A few studies claim benefits from watching a movie to an individual or group of patients suffering from one or another disorder. This probably affords temporary relief to some sufferers, but I’m dubious about long-term relief. I have, however, recommended a film when I think it might energize insight, but not often, and only when I know the client well.

I once treated a gifted young writer who developed a catastrophic depression when his wealthy fiancée suddenly broke off their engagement. Her tycoon father witheringly criticized my patient’s working-class background and occupation. She had fled the shadow of his iron will to marry her patient, only to quail before her father when he threatened to disinherit her.

Several months later my patient met another woman with a striking physical resemblance to his former fiancée but a totally dissimilar personality. No fool, she had begun to suss out the distorted basis for their relationship and was backing off. When his desolation bred suicidal fantasies, I recommended Alfred Hitchcock’s Vertigo (1958).

Hitchcock’s masterpiece devolves around a retired detective’s (James Stewart) desperate attempt to remake—Pygmalion-like—a shop-girl (Kim Novak) into a simulacrum of the beguiling, supposedly suicidal high-society wife he had been asked to protect by her (unknown to him) murderous husband.

Stewart’s character had fallen in love with her, then suffered a devastating depression after being unable to save her from jumping to her death, due to the acrophobia that had compelled his retirement. The detective eventually discovers he’s been cruelly hounded: the socialite knew and the shopgirl are the same woman; the latter used, then discarded by the husband after he killed the “original.”

Exploring my patient’s reaction to Vertigo was crucial in grieving his loss. He eventually recognized that long-standing irrational feelings of not being “good enough” had enforced his conviction he had been responsible for his fiancée’s reckless abandonment. “Just like Stewart, I fooled myself trying to make a new lover into a mirror of my fiancee,” he concluded, “it was like trying to fix an amputated arm by shoving a prosthesis into a bloody socket.”

My most memorable case in which probing a film was central to effective psychotherapy was that of a 35-year-old Vietnam vet. Despite an apparently healthy return to civilian life, he was increasingly ravaged by lifelong allowed post-traumatic psychopathology.

He came from a tough urban ghetto. When he was arrested for petty theft at 18, the judge offered him enlistment as an alternative to jail. He turned out to be an exemplary soldier, rose quickly through the ranks, and eventually commanded a platoon in Viet Nam.

He was a huge fan of war movies, particularly Objective, Burma! (1945), in which Errol Flynn headed a dare-devil commando team. Identifying strongly with the hero’s unflagging competence and love for his men, he was certain he could bring his “guys” back home safely.

He nearly did, until an ambush during their last week of active duty, killed or grievously wounded most of his outfit. He escaped harm, rendering his guilt even more intolerable.

He finally entered treatment, convinced that “a man like Errol Flynn would have gotten us through—and I wasn’t that man.” Over several years of psychotherapy, my patient discovered that Flynn’s unflagging resolute captain represented a neurotic ego-ideal, woven from adolescent omnipotent fantasies.

Like any therapist, I’m not immune to the pitfalls of countertransference. It’s especially difficult to avoid gabbing about movies with a fellow addict who just happens to be my patient. He or she may be creating a diversion so as not to deal with the deeper stuff. But I admit to having taken the bait on occasion, at least temporarily.

I acknowledge this ad hominem rationalization, but I suspect the Founding Father himself went on and on about some item from his enormous collection of antiquities with the Wolf Man, Rat Man, and company, beyond the object’s therapeutic merit. As far as I know, neither the earlier hagiographers nor acrimonious bashers from the Freud wars have had anything to say on that subject.

Dr. Greenberg practices psychiatry in Manhattan, New York. He continues to publish frequently on film, media, and popular culture. For many years, his cinema column appeared in Psychiatric Times. He has appeared frequently on national and international network and cable television programs including Good Morning America, Today, CBS Evening and Sunday News, PBS, CNN, Showtime, and BBC-TV.

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From the Editor

Continued from page 2

new discovery as the answer to the mystery of life, and all that was left to do was fill in some of the details. Today, there are more questions than answers as to how the human genome of 3 billion base pairs produces a living, breathing, and conscious person. Many mysteries wait to be solved, including the answer to why only 2% of the human genome codes for proteins—the rest codes for small RNAs whose roles we are just beginning to glimpse. Layer on to this the evolving field of epigenetics, and your mind will truly be blown (more on this in this future editorial).

For us in psychiatry, it has been a mere 30 years since we have redefined the human brain from being a “black box” to a structure of circuits containing 80 billion neurons and approximately 100 trillion synapses—fondly named the connectome—which makes each person beautifully unique. So yes, we have come a long way in understanding brain structure and function, and in our ever-evolving armamentarium of psychiatric treatments—medications, evidence-based psychotherapies, neurorehabilitation, vocational support, psychopharmacology, and preventive health. Equally important are the clear brain and body benefits of a good night’s sleep, exercise, healthy social relationships, good nutrition, stress reduction, laughter, lifelong learning, employment, and feeling connected to something greater than oneself.

However, as history has taught us, the discoveries of today will become the fossils of tomorrow. I do not say this to be bleak, but rather to remind us that our creative minds must always be open to new treatments that result from a new understanding. Each issue of Psychiatric Times serves as a bookmark in time to declare where we are and some day to reflect back on where we have been. Finally, we must continue to advocate for our patients, support our colleagues, erase stigma, and educate politicians/insurers/policy makers about the primal necessity of global mental health.

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team, but no other specific rehabilitation was provided beyond that which occurred as part of coordinated specialty care in the clinics.

Global cognition improvement was seen in the TCT group at immediate post-training assessments. Participants who completed at least 20 hours of TCT showed significant improvement in positive symptoms at 6-month follow-up compared with CG completers. Modeling of outcomes revealed that lower baseline global cognition and a higher level of education predicted greater improvement in global cognition after TCT.

In a subgroup of participants who agreed to undergo serial imaging, Ramsay and colleagues saw a significant positive correlation between left thalamic volume and increased global cognition in the TCT group (n = 22) and a negative trend in the computer games CG group (n = 22). Lower baseline symptoms were related to both left thalamic volume preservation and improvements in global cognition following the training.

This intervention was also studied in adults with persistent illness (average age, 40 years) and demonstrated improved cognition in the TCT group and higher serum brain-derived neurotrophic factor (BDNF) levels. Moreover, magnetoencephalographic and fMRI findings were consistent with enhanced cortical activation patterns during early sensory processing and prefrontal executive functions. Patterns of association were seen between enhanced cognition and/or cortical functioning and longer-term functional gains.

Cognitive training is a highly scalable and low-cost intervention provided clinicians can offer the necessary degree of support.

Future directions
Are we ready to prescribe cognitive training to patients? It is one thing to have a highly promising evidence base emerging from clinical trials; it is another to know how to translate those findings into real-world treatment settings where models of implementation and reimbursement for cognitive remediation and/or cognitive training approaches are few and far between. Tools and education for clinicians that can allow them to assess and understand patterns of cognitive dysfunction in their patients are needed.

Cognitive training is a highly scalable and low-cost intervention, provided knowledgeable clinicians and staff can offer the necessary degree of support and guidance to patients. Ideally, cognitive training can be offered either as stand-alone cognitive treatment or as part of a broader enriched “remediation” program, depending on the needs of the individual; some individuals will be highly reliant on the structure and support of a formal multi-modal program and require group support, skills-building, etc, while others will be able to engage remotely, perhaps assisted only by an app that provides remote coaching (currently under study in our clinical trial NCT02782442).

Interested clinicians and consumers can consult Psyberguide.org, a non-profit organization whose mission is to help consumers choose effective and accessible mobile health technologies, including cognitive training programs (Psyberguide.org offers ratings on credibility, user experience, and the clarity of an app’s privacy policy). As we continue to refine our scientific understanding of cognitive training interventions for people with psychotic disorders, it may behoove us to begin to develop the programmatic infrastructure that allows us to assess cognition as a key treatment target for our patients.

Dr Vinogradov is Professor and Department Head, Donald W. Hastings Endowed Chair, Department of Psychiatry, University of Minnesota Medical School, Minneapolis, MN.

Dr Vinogradov reports that she is on the Speakers’ Bureau for Akirinse and Mindstrong.

References
Ketamine for Stress-Related Psychopathology and Suicidality: A Brief Update

The serendipitous discovery of ketamine’s rapid-acting and robust antidepressant effects has been hailed as “arguably the most important discovery [in neuropsychiatric research] in half a century.” However, the optimism regarding ketamine’s rapid-acting antidepressant (RAAD) effects in stress-related psychopathology, including suicidality, is tempered by concerns about long-term safety; the lack of a reproducible biomarker of target engagement/validation; and the need to extend the durability of clinical benefits, reduce adverse effects, and limit abuse potential. Nonetheless, the discovery—and replication—of ketamine’s antidepressant effects has prompted a paradigm shift in our understanding of the neurobiology underlying stress-related psychopathology and in our approach to drug development for associated symptom constellations.

The bleak landscape of traditional antidepressants
Since the early 1950s, tricyclics, monoamine oxidase inhibitors, and SSRIs have been used to treat depression and other stress-related disorders. These drugs were developed under a monoaminergic hypothesis that postulates psychopathology is due to a functional deficiency in monoaminergic neurotransmitters (eg, serotonin, dopamine, norepinephrine). Thus, the mechanism of action for traditional antidepressants is to elevate synaptic availability of these neurotransmitters.
Although these drugs work very well for some patients, they have limitations. Approximately two-thirds of patients do not achieve symptom remission with a single medication trial, and among the one-third who do, rates of sustained remission are low. Furthermore, even when these agents are effective, they are slow-acting antidepressants (SAADs) with a delayed onset of action; thus, it can take weeks to months before patients experience clinical benefit.

This latency period significantly increases the risk of suicide and self-harm as well as other destructive behaviors, including self-medication with drugs and alcohol. With each failed medication trial, the likelihood of finding an effective treatment declines, further increasing risk. Moreover, SAADs often fall short of treating the full spectrum of symptoms for many patients; consequently, even when some improvement is noted, refractory symptoms persist, including suicidal ideation and cognitive impairment.

The landscape is perhaps even bleaker for bipolar disorder or PTSD because there are significantly fewer FDA-approved pharmacologic options for these disorders. With the exception of clozapine, which is approved by the FDA to target suicide risk in patients with schizophrenia, no medications are specifically indicated for suicidality.

**Ketamine’s RAAD effects in stress-related symptoms and suicidality**

Multiple studies have supported the short-term efficacy of ketamine—and more recently, one of its two enantiomers, S+ (esketamine)—for stress-related psychopathology. Significant benefits have been demonstrated for suicidal ideation and PTSD, even after adjusting for simultaneous reductions in depressive symptoms. Ketamine was associated with increased clinical response and remission relative to comparators (e.g., saline/placebo, midazolam) in individuals with either MDD or bipolar depression, suicidality, and PTSD, regardless of treatment-resistant status and of whether study participants were medicated. In addition, the suspected neurobiological effects of ketamine were further supported by the relatively consistent response across studies: improvement within 4 hours, peak response at about 24 hours, and efficacy for approximately 7 to 10 days, as well as the maintenance of efficacy through repeated treatment (Figure 1).

Similar onset and duration of clinical benefit have been shown for suicidal ideation: rapid-acting antisuicidal (RAAS) effects occurred within 24 hours and persisted approximately 1 week. A recent trial that compared the RAAS effects of ketamine with those of the active comparator midazolam found ketamine was superior in promoting rapid and robust improvements in suicidal ideation. These improvements were maintained for up to 6 weeks with an additional optimized standard pharmacologic intervention.

Based on the promising results of intranasal esketamine trials the FDA has designated it as a “breakthrough therapy.” While these results are encouraging, further investigation will be required to establish ketamine’s efficacy as well as to determine how best to extend the durability of effects and to reduce adverse effects and risk of abuse.

**Clinical anecdotes from subjective reports**

Findings indicate that ketamine’s robust RAAD and RAAS effects have a positive downstream effect in which the improvement in symptoms, especially in lassitude and negative mood and cognitions, kick-starts therapeutically beneficial practices. In addition to self-initiated engagement outside the study, the behavioral activation of participating in a clinical trial (e.g., the structure provided by study visits, required outing, engaging with research staff) seems to be highly therapeutic as well.

**CASE VIGNETTES**

One man in his early 50s who had struggled with treatment-resistant MDD for several decades reported a single infusion of ketamine gave him the boost he needed to re-engage in hobbies and to feel invigorated for both work and family life. The day after his infusion, he reported that he had slept well, cooked his family breakfast, practiced an instrument, and planned to walk his dog in the evening—all of which he enjoys but has not had the motivation for recently. Although he reported a re-emergence in some symptoms at 2-week and 4-week follow-up, he experienced ketamine-promoted re-engagement in mood-enhancing activities, which helped extend the effects.

A Vietnam Veteran with treatment-resistant PTSD and chronic suicidal ideation, said he had attempted to take his own life on three occasions since the late 1960s, when he experienced significant trauma in combat. Following the ketamine infusion, he was “totally stunned to wake up without a single idea about suicide” and reported a significant reduction in negative mood and cognitions, specifically guilt, shame, and related self-talk. He was able to talk with his spouse about things he had never discussed previously, which not only was cathartic for him, but also brought them closer together. He reported a slight re-emergence in overall symptoms, including suicidal ideation at the 4-week follow-up visit, but noted the “memory of hope and better days” kept him pushing forward.
Until recently, ketamine has been given only in the context of research studies. However, as evidence of its effects has continued to build along with data that suggest the drug is well-tolerated—despite concerns about unknown long-term effects, short duration of effects, and abuse potential—medical professionals with prescribing privileges have started offering the drug as an off-label treatment. Ketamine “boutique” clinics are opening across the country.

A current challenge is that most health insurance companies do not cover the high costs of off-label ketamine dosing. Patients for whom the medication is effective are concerned about how to continue treatment, especially if they do not have the finances for private-pay options. Similarly, health care providers are concerned about the options for those who respond to ketamine as well as for those who do not.

A consensus statement from the American Psychiatric Association Research Task Force on Novel Biomarkers and Treatments provides a good summary of the promise and limitations of off-label ketamine treatment.7 Although no clinical practice guidelines exist for the off-label administration of ketamine, the consensus statement offers an overview of appropriate training for prescribers, treatment setting and available facilities and resources (eg, blood pressure monitor, crash cart), and patient considerations (eg, safety eligibility such as cardiovascular risk factors or history of psychosis) as well as the challenges and limitations of the drug, including abuse potential, adverse-effect profile, and limited durability of effect (Figure 1).

A synaptic model of chronic stress pathology
Psychopharmacologic drug development and neuropsychiatry are undergoing a paradigm shift from the monoamine neurotransmitter systems toward the glutamatergic system and glutamate modulators for the treatment of stress-related psychopathology. Ketamine, a noncompetitive, high-affinity, N-methyl-D-aspartate receptor (NMDAR) antagonist, has served as the poster child for this new generation of research and drug development. Landmark preclinical and clinical studies that provided the first solid evidence of RAAD-like effects began an avalanche of research, including trials of ketamine and other glutamatergic drugs as well as those that support a glutamate- or synaptic-based hypothesis of chronic stress pathology (CSP).9,10,11 Early studies of SAADs altering NMDAR binding led to the hypothesis that the downregulation of NMDAR function may be a common pathway of antidepressant action.12 At the same time, we had the first evidence of gray matter volume loss in stress-related psychopathology, which appeared to parallel dendritic atrophy observed with chronic stress in rodents.13 These converging data suggested that downregulation of excess glutamate may exert antidepressant effects, which led to the question of whether ketamine’s RAAD effects may be due to the blockage of NMDARs and subsequent inhibition of glutamate neurotransmission.

In contrast to this inhibition model, mounting evidence also hinted at a neurotrophic hypothesis of stress-related psychopathology, in which chronic stress and depression are associated with a deficit in brain-derived neurotrophic factor (BDNF).14 Other findings suggested that administration of subanesthetic ketamine produces transient activation of glutamate neurotransmission. This α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor–dependent activation was found to increase BDNF levels and promote RAAD-like effects in rodent models.

It makes sense to consider psychopathology through the lens of the glutamatergic system because glutamate is the most prevalent excitatory neurotransmitter in the brain. Furthermore, synaptic glutamate neurotransmission is cardinal in emotion, cognition, and behavior—all phenomena inextricably linked to psychopathology. Clinical findings support dysregulated glutamate neurotransmission in cortical and limbic areas as well as variance in glutamate content in individuals with stress-related psychopathology relative to those who are psychiatrically healthy.15 It is hypothesized that the pattern and location of these synaptic alterations interact with individual and environmental characteristics to affect the clinical presentation and constellation of symptoms. Focus on glutamate-related neural remodeling and synaptic plasticity has led to a synaptic hypothesis of CSP.

Chronic stress has been associated with both synaptic potentiation and neuronal hypertrophy in brain regions including the amygdala and nucleus accumbens, as well as synaptic depression and neuronal atrophy in the prefrontal cortex, and hippocampus. The synaptic alterations in the hippocampus and prefrontal cortex are thought to be secondary to stress-induced changes in glutamate release and reuptake and astroglial loss, resulting in sustained

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**Figure 2. The cyclical effects of chronic stress pathology in stress-related psychopathology and suicidality**

[Diagram showing the cyclical effects of chronic stress pathology in stress-related psychopathology and suicidality]

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**Common questions and challenges**

One of the most common questions asked by potential study participants and treatment providers is, “What do we do if ketamine works—what’s next?”

An Army Veteran in his mid-40s endorsed only relatively minor improvements on formalized measures of PTSD symptoms. However, he noted that his quality of life and level of irritability improved significantly after he received a single open-label dose of ketamine (0.5 mg/kg). The treatment increased his cognitive flexibility, reduced his rigidity, and diminished the sense that any minor disruption in his plans was “catastrophic” and would throw his entire day (sometimes up to a week) into unrest. He reported that following the infusion, he was much more able to “roll with the punches” and “take things as they come.” At a 4-week follow-up visit, he indicated this change in emotion, cognition, and behavior had been maintained despite other symptoms that resurfaced.

As in the last vignette, some of the meaningful improvements reported by participants are not necessarily captured by routinely used clinician-administered or self-report measures. For example, another interesting, and challenging, phenomenon is that sometimes patients report guilt, shame, and/or frustration that their symptoms improved so dramatically in such a brief period. They feel something must be wrong with them if they can feel so much better, if it is this “easy.” Some patients report they unintentionally “blunt” the clinical benefit of ketamine because they are worried about when it will end and are “waiting for the other shoe to drop.”

A clear informed consent process is paramount, for both research and clinical settings. Ideally, the participant’s mental health care provider should be involved early, and patients should be encouraged to discuss the pros and cons of ketamine with family members or other close confidants. Overall, we have found that patients are glad they participated and are willing to seek out alternative routes for additional doses, either through research or clinical settings, or to explore other treatment options. We have not had patients who reported seeking out illegal means of obtaining ketamine.
elevations in extracellular glutamate. This precipitates reduced spine density, dendritic retraction, and branching in the prefrontal cortex as well as altered synaptic strength and excitotoxicity. The dysregulation in glutamate release and glucocorticoid signaling, together with reduced glutamate uptake and astroglial deficits, are suspected to paradoxically maintain elevated levels of extracellular glutamate despite chronic stress-induced reductions in synaptic glutamate neurotransmission.

Stress-induced synaptic hyperconnectivity in the nucleus accumbens is associated with dysregulation in monoaminergic neurotransmitters, whereas hypoconnectivity in the prefrontal cortex is associated with glutamate excitotoxicity and dysregulation. MRI studies have demonstrated that the reversal of synaptic deficits produces antidepressant-like effects and both RAADs and SAADs can reduce synaptic connectivity in the nucleus accumbens while alternately increasing connectivity in the prefrontal cortex. MRI findings have also shown reduced volume in the hippocampus and prefrontal cortex of individuals with SAAD/monoaminergic treatment-resistant depression, particularly those with impaired glutamate and γ-aminobutyric acid levels.14,15

Ketamine-induced neural alterations provide the opportunity to examine putative biomarkers underlying CSP and RAAD treatment response.

The synaptic model of CSP has some important components:

1. The duration of stress response—as opposed to the duration of stress exposure—is critical, and the distinction between acute and chronic stress is paramount. Although there is significant individual variability in stress response and resilience, exposure to a single extreme stressor or trauma may lead to a sustained or “chronic” threat response, whereas ongoing or repeated escapable, manageable, or predictable stress exposure may lead to acute transient responses.

2. Two independent pathways—hyperconnectivity in the nucleus accumbens and hypoconnectivity in the prefrontal cortex and hippocampus—may contribute to stress-related psychopathology. Patients with monoamine-based pathology show localized nucleus accumbens elevations in synaptic gain and BDNF, lack of amino acid impairment, enhanced response to monoaminergic SAADs, and increased volume in the nucleus accumbens. Patients with amino acid–based pathology demonstrate prefrontal cortex synaptic loss and excitoexcitotoxicity, amino acid impairment, and resistance to monoaminergic SAADs and have gray matter deficits in the hippocampus and prefrontal cortex (Figure 2).

Research on glutamate release inhibitors, NMDAR antagonism, and glutamate neurotransmission activation has yielded promising results, yet ketamine and other glutamatergic drugs have notable limitations for mainstream use that require further study. Moreover, it is yet to be determined whether synaptic loss and dysconnectivity represent predisposing risk factors, an outcome of stress exposure, or factors that perpetuate psychopathology. The synaptic model posits that CSP is a common pathway across many psychopathologies and that targeting synaptic loss and dysconnectivity may provide mechanistically novel RAADs with the potential to improve the lives of patients with stress-related psychopathology, including suicidality.

Ketamine as a treatment and a tool

Based on this synaptic model of CSP, ketamine’s suspected mechanism of action provides a unique opportunity to:

- Advance our understanding of CSP
- Investigate our ability to reverse neural alterations in CSP and the cognitive, emotional, and behavioral implications of doing so
- Explore ketamine-affected biomarkers of CSP
- Inform novel drug development.

Two ketamine-induced alterations in glutamate neurotransmission may underlie its RAAD effects: (1) an acute burst of glutamate leading to transient prefrontal activation of glutamate neurotransmission and (2) a sustained increase in prefrontal synaptic connectivity. Brief surges of prefrontal glutamate precipitate multiple intracellular processes that ultimately lead to increased synaptic connectivity in the prefrontal cortex approximately 24 hours after a subanesthetic dose of ketamine. Figure 1 shows the suspected pathway of ketamine’s action beginning with postsynaptic activation leading to a glutamate surge and BDNF release, activation of mammalian target of rapamycin signaling, and elevations in synaptic strength and protein synthesis.

Evidence from MRI studies has repeatedly demonstrated reduced frontal cortex global brain connectivity in stress-related disorders and suicidality, which suggests that this may be a viable biomarker of CSP.15–17 Human mechanistic studies further support this notion by directly coupling prefrontal cortex global brain connectivity to glutamate neurotransmission, ketamine administration to increased prefrontal cortex global brain connectivity, and this ketamine-induced normalization in connectivity to the RAAD effects and treatment response.14,15 Ketamine has been seen to influence gray matter volume—with increases in the hippocampus and decreases in the nucleus accumbens—at the peak of treatment response.14,15 These ketamine-induced neural alterations in glutamate neurotransmission, global brain connectivity, and gray matter volume provide the opportunity to examine putative biomarkers underlying CSP and RAAD treatment response.

References

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For immediate consideration, please contact Renee Theobald, at Renee.Theobald@hackensackmeridian.org or call: 732 751-3597

HackensackMeridianHealth.org

Outpatient Adult and Child Psychiatrists are needed for Stanislaus County Behavioral Health & Recovery Services, in the Central Valley less than two hours from San Francisco and Yosemite. Recovery-oriented treatment provided in a multidisciplinary setting with friendly and dedicated staff members. Recently revised rates with full malpractice coverage and pension plan (PARS) as a Personal Service contractor with an income potential of over $ 325 K per year for adult psychiatrist and over $355 K per year for child psychiatrist for F/T work.

P/T options and the opportunity to combine Tele-Psych with limited onsite work are also available. Excellent work environment with NO Call Requirement, lower than average case load and comprehensive nursing & ancillary support makes this a very pleasant and rewarding opportunity. J1 applicants are welcome.

Fax CV to Bernardo Mora, MD at (209) 558-4326 or Email: bmora@stanhsrs.org

Psychiatrist Position

J-1 Visa Opportunity in California

Imperial County Behavioral Health Services is currently recruiting for a full time psychiatrist. Imperial County is located 90 miles by freeway to the city of San Diego to the west, and 90 miles to Palm Springs to the north. Located in a rich farming area, Imperial County has a population of 180,000 and borders with Yuma, Arizona and with the cosmopolitan city of Mexicali, Mexico population 1.2 million. San Diego State University maintains a satellite campus in Calexico and there are a number of private and public universities located in Mexicali, the state capital of Baja California Norte. Imperial County’s location and diversity make it the perfect place for a psychiatrist to relocate under the J-1 Visa program or for any reason.

The position pays a highly competitive salary, including health benefits for you and your family, and requires no hospital work and minimal after hours work freeing you up for more leisurely activities.

The successful candidate diagnoses and treats patients with mental, emotional, and behavioral disorders. Qualified candidate must have CA medical license or ability to obtain.

Send CV to Imperial County Behavioral Health Services, 202 North 8th Street, El Centro, CA 92243.

J-1 applicants welcome.

For additional information, please contact:
Kristen Smith (442)265-1606
kristensmith@co.imperial.ca.us

Vituity is changing lives with innovative new programs. We are hiring part-time and full-time Emergency & Inpatient Psychiatrists in California:

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- San Francisco Bay Area
- Sacramento Area

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California Department of State Hospitals

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We are currently recruiting psychiatrists at our five locations:

Practice and Benefits:
- Annual salaries to the high $200,000s
- Flexible workweek options may be available
- Voluntary paid on-call duty
- Substantial continuing medical education
- Generous defined-benefit pension
- Psychopharmacology support by leading experts and established protocols

- Medical, dental and vision benefits
- Private practice permitted
- Retiree healthcare
- Psychiatrist-led treatment teams
- Patient-centric, treatment first environment
- Relocation assistance may be available

To find out more, please contact Laura Dardashti, MD. at (916) 654-2609. You can also email us at DSH.Recruitment@dsh.ca.gov or visit our website at www.dsh.ca.gov

Central New York Psychiatric Center


Seeking Psychiatrists!

Central New York Psychiatric Center (CNYPC) recognizes that our employees are our greatest resource. We are seeking motivated psychiatrists to help promote hope, resilience, and recovery within a culture of safety that employs a team approach. CNYPC is a dynamic organization that provides comprehensive forensic mental health services through a continuum of care at its inpatient setting, located in Central New York, and in the Correctional System throughout New York State. CNYPC is fully accredited by The Joint Commission.

Benefits:
- Recent inpatient salary increase: $247,087 - $268,311.
- Psychiatrist Loan Repayment Program offering up to $150,000 over 5 years.
- Flexible work schedules. Private practice permitted.
- Tele-psychiatry positions available at our VTC Suites.
- 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 NYS, within commuting distance of most major cities.

For more information, contact Melinda Carey, HR Specialist, at 315-765-3360 or Melinda.Carey@omh.ny.gov
Chief Medical Officer – Community Healthlink
Worcester, MA

UMass Memorial Health Care’s Department of Psychiatry and its Community Healthlink (CHL) member institution is looking for a chief medical officer to help lead the largest provider of mental health services in Central Massachusetts.

The position involves supervision of a large group of professionals and participation in the executive team’s strategic, program and organizational development efforts. The ideal candidate will have a demonstrated commitment and passion for community psychiatry and an interest in a leadership role in advocating and promoting the wellbeing of traditionally underserved populations.

CHL has a long tradition of bringing excellent mental health and substance use disorder services to our city and region, from its inception as a community mental health agency to its current role as a key member organization at UMMHC. Its 1300 employees serve over 22,000 individuals each year and its programs assist patients across the life span. Medical staff are faculty members of the UMass Department of Psychiatry and employees of the medical group practice—they are vital contributors to the department’s missions of training, research, and clinical excellence. We believe this position will be a terrific opportunity for individuals committed to serving their community through the provision of high quality psychiatric care as part of mission driven team

To learn more about our Community Healthlink locations, please visit our website
http://www.communityhealthlink.org/chl/

Interested applicants should submit a letter of interest and curriculum vitae addressed to:
Alan P. Brown, MD
Vice Chairman of UMMS Department of Psychiatry for BH Integration and Population Health
Clinical Professor of Psychiatry, Family Medicine and Community Health
c/o: Jessica Saintelus, Physician Recruiter
Jessica.Saintelus@umassmemorial.org

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INDIANA

NORTHWEST INDIANA!!

Excellent opportunity for adult psychiatrist interested in optimal setting for practice of community psychiatry; commutable from downtown Chicago.

Regional Mental Health Center is a private non-profit mental health center that has successfully served Indiana for over 30 years. Experienced and collegial group of 12 mostly full-time psychiatrists, an extremely favorable malpractice environment. OP work, call q 12 wks. Regional is a leader in psychiatrist-directed integrated care services. Incentive bonus available, full benefits.

Please contact Kobi Douglas, MD: kobidouglas@regionalmentalhealth.org 219 736-7232

CALL FOR MORE INFORMATION
(203) 523-7026

MICHIGAN

Sparrow

Psychiatry Position with Sparrow Medical Group

Sparrow Medical Group (SMG), a multi-specialty physician group and the premier physician organization of Sparrow Health System (SHS), located in Lansing, Michigan, is seeking a dynamic BC/BE psychiatrist for an adult inpatient position. Position is hospital-employed and offers excellent compensation and benefits including relocation assistance, 401(k) with matching funds, generous CME benefits and malpractice insurance that includes tail coverage. Learn more about this position by contacting:

Barbara Hiliborn, Manager Provider Recruitment Office: 1.800.968.3225 Email: barbara.hiliborn@sparrow.org
Visit our website at www.sparrow.org
More information on the Lansing area can be obtained at www.lansing.org

NEW YORK

Inpatient Psychiatrist at Attractive Community Hospital Setting – Huntington Hospital

Huntington Hospital, an award-winning community hospital that serves as one of Northwell Health’s western Suffolk County anchors on Long Island, NY, is seeking an inpatient psychiatrist for its 21-bed general psychiatry unit. Known for its friendliness and commitment to excellent care, Huntington Hospital enjoys a high degree of staff satisfaction and collegiality. The inpatient psychiatry unit’s multidisciplinary team serves a heterogeneous population of general psychiatry patients, and is comprised of psychiatrists, nurse practitioners, nurses, and social workers.

In addition to a manageable inpatient caseload and contributing to the life of the hospital through voluntary participation in committee-work; the successful candidate will also have the opportunity to engage in the diverse and innovative activities of Northwell’s Behavioral Health Service Line, including system-wide quality and performance improvement initiatives, telepsychiatry, emerging digital psychiatry applications, development of data-driven dashboards, refinement of a behavioral health EHR, and medical student and allied health professional trainee supervision and education.

Graduating residents and fellows are welcome. Employment package includes academic appointment at the Donald and Barbara Zucker School of Medicine at Hofstra/Northwell; a highly competitive salary; perquisites that include academic conference and organization dues cost reimbursement, college and graduate school contributions for eligible dependents, and comprehensive benefits, generous paid time off, and retirement plans. Additional earning potential exists via faculty practice and internal moonlighting opportunities.

Huntington Hospital is located approximately 40 miles from Manhattan. The area offers affordable housing options in the desirable hamlet of Huntington and in nearby highly-regarded suburban communities with excellent school systems and access to many community resources (e.g. parks, beaches, museums) and appealing shopping and restaurant choices.

Northwell Health is New York State’s largest health care provider and private employer, with 23 hospitals, about 650 outpatient facilities and nearly 15,000 affiliated physicians. We care for over two million people annually in the New York metro area and beyond, thanks to philanthropic support from our communities. Our 66,000 employees – 15,000-plus nurses and 4,000 employed doctors, including members of Northwell Health Physician Partners – are working to change health care for the better. We’re making breakthroughs in medicine at the Feinstein Institute for Medical Research. We’re training the next generation of medical professionals at the visionary Donald and Barbara Zucker School of Medicine at Hofstra/Northwell and the Hofstra Northwell School of Graduate Nursing and Physician Assistant Studies. For information on our more than 100 medical specialties, visit Northwell.edu.

For further information please contact the Office of Physician Recruitment at OPR@northwell.edu.

www.psychiatrictimes.com
We Want You to Join Our Behavioral Health Team!

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

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

Emergency Opportunity

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

Adult Outpatient Opportunity

• BE/BC provider with training/experience in a variety of mental health treatment conditions as well as Chemical Dependency and Substance Abuse. Candidate with experience in treatment of Bipolar Disorder, Borderline Personality Disorder, and Mood Disorders is preferred. Additionally, ECT training and experience is highly desirable. Well established adult team is flexible and transparent for either or both inpatient and outpatient services. Clinic hours are Monday - Friday with limited call

Child Outpatient Opportunity

BE/BC Child & Adolescent providers. The current structure is for 90% outpatient Monday through Friday work schedule. We offer best in class compensation plus generous benefits including Paid Malpractice, CME Time and Allowance, Accrued Paid Time Off, 403(b) match and 457(b), Health, Dental, and other desirable benefits.

Please contact Suzy Cobb, Physician Recruiter for more details at 800-815-1889 or scob2@capefearvalley.com.

North Carolina

We offer a variety of behavioral health opportunities in attractive locations.

Pennsylvania

The Penn State Hershey Medical Center Department of Psychiatry is currently recruiting board eligible/certified psychiatrists for inpatient and outpatient positions in both adult and child psychiatry. We are a growing, vibrant department in a strong academic medical center. We host specialty clinical and research programs, including research that crosses the translational spectrum. Our educational programs include adult psychiatry residency, child fellowship, psychology internship, externship and post-doctoral fellows. We have a strong collaboration with basic and clinical science in other neuroscience disciplines across several Penn State campuses. With our clinical partner, the Pennsylvania Psychiatric Institute, the Department staffs several outpatient and partial hospital programs for children and adults, 89 inpatient beds, ECT and other neuromodulation services, specialty sleep and eating-disorders programs, and expanding psychiatric consultation and integrated care programs for Hershey Medical Center.

Successful candidates should have strong teaching as well as clinical skills and, optimally, potential for scientific and scholarly achievement. We offer an attractive compensation package commensurate with qualifications, with opportunities for tenure-track positions.

For consideration, send your CV to:

Jenna Spangler, Physician Recruiter
Phone: 717-531-4271 Email: jsplangler2@pennstatehealth.psu.edu

The Penn State Milton S. Hershey Medical Center is committed to affirmative action, equal opportunity and the diversity of its workforce. Equal Opportunity Employer – M/W/D

Virginia

Psychiatrist Opportunity

Southwestern Virginia Mental Health Institute is located in Marion, Virginia, sitting in the heart of the Blue Ridge Mountains. Our 179-bed behavioral health facility offers an exciting career in a wide range of interesting pathology in psychiatric treatment while providing a highly desirable work-life balance.

We have opportunities in our inpatient setting for Psychiatrists for our Adult Admissions and Geriatric Units. These positions are employed positions offering a competitive salary with generous state benefits and paid malpractice insurance, loan repayment, CME stipend/leave, sign-on bonus, and relocation allowance. No on-call required, with uncompensated on-call available.

If you are licensed or eligible for licensure in Virginia, and have completed a psychiatric residency, please send your current CV to kim.sayers@dhlsvirginia.gov or you may contact a member of our Human Resources staff at 276-783-1204 to discuss this opportunity.

We invite you to join a team of dedicated physicians and loyal staff who are committed to promoting a life of possibilities for all Virginians.

For more information, please visit:

www.swmhii.dhlsvirginia.gov
www.smythcountyorg
www.abingdon.va.gov

(203) 523-7026

Washington

Overlake Psychiatry is a 5 person office located in Bellefield Office Park in Bellevue, WA, that has been in existence since 1989. Bellevue is a convenient location with potential for a large number of new patients. We are 5 solo providers who share overhead and staff expenses. All of us are either retiring or moving by the end of October 2019. We receive many more new patient referrals than we are capable of seeing.

We all have busy practices and are offering a turnkey operation of patients (assuming it is a mutual fit), waiting room furniture, equipment including phones, printer, fax, computer, supplies, etc. Our current lease runs through October 31, 2019, but it currently can be renewed close to mid April.

If interested, please contact us at 425-454-0255 or email at ziggyweil@gmail.com

Wisconsin

Psychiatrist

Clinical excellence and quality living! Winnebago Mental Health Institute (WMHI) is a 280 bed psychiatric facility associated with Medical College of Wisconsin’s North East Wisconsin Psychiatry Residency. We are seeking a Board Certified/Board Eligible Psychiatrist who wants to work with a Multidisciplinary Treatment Team to treat acutely ill Civil Patients and/or Forensic Patients. A strong commitment to excellence in clinical care and education of Residents, Medical Students and students/ interns of all clinical specialties makes WMHI a great place to practice. Excellent fringe benefit package, strong collegial support, paid call, and a beautiful campus enhance your work days.

WMHI is located near Oshkosh, Wisconsin, which is the center of the Fox River Valley, one of the fastest developing areas of Wisconsin. Four seasons with all the outdoor opportunities of each, cultural and sports venues, outstanding public and private schools and three universities in the area make this a great place to raise a family. In 1 1/2 hours you can be in Milwaukee, Madison, the Wisconsin Dells or “up north”. Information on WMHI can be found at http://www.dhs.wisconsin.gov/MH_Winnebago.

For application instructions, go to www.wisc.jobs and search for Psychiatrist (Job Announcement Code: 17-02966).

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