When Dawn Sims picks up her curbside groceries, she sanitizes her packaged products with chlorhexidine, a medical-grade disinfectant. Otherwise, she only eats fresh foods that can be washed, zapped in the microwave, or peeled.

Sims, aged 50 years, resides on a 20-acre property with her husband and mother. The property consists of 2 buildings, 30 ft apart. Sims and her husband live in one; her mother, aged 79 years, lives alone in the other. She loved being close to her mother—until COVID-19 hit.
The 2021 Annual Psychiatric Times™ World CME Conference™ is the perfect educational venue for addressing knowledge gaps related to the application of new strategies in psychiatry to real-world clinical practice.

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- Major depressive disorder
- Substance use disorders
- Bipolar disorder
- Schizophrenia
- And more!

HOT TOPICS FOR 2021

- Helping patients deal with grief
- Wellness for our patients and for ourselves
- How to teach neuroscience
- Telemedicine and its impact on our practice
- Comorbidities in mental health

PROGRAM CO-CHAIRS

Anita Clayton, MD
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Sanjai Rao, MD
Associate Clinical Professor of Psychiatry University of California, San Diego Psychiatrist VA San Diego Healthcare System San Diego, CA
9:05 AM
Treatment-Resistant Depression
Michael Thase, MD

9:30 AM
Postsession Survey and Audience Q&A
Moderator: Sheldon H. Preskorn, MD
Panelists: Michael Thase, MD; and Sidney Zisook, MD

9:50 AM BREAK

SPECIAL REPORT ON BIPOLAR DISORDER
Moderator: Roger McIntyre, MD

10:20 AM
Presession Survey
Roger McIntyre, MD

10:30 AM
Medical Crossfire®: Should Bipolar Depression Be Treated With Antidepressants?
Moderator: Roger McIntyre, MD
Panelists: Joseph F. Goldberg, MD; and Nassir Ghaemi, MD, MPH

11:00 AM
Bipolar Disorder: Early Intervention Strategies
Melissa DelBello, MD, MS; and Nassir Ghaemi, MD, MPH

11:15 AM
Maintenance Therapy in Bipolar Disorder
Joseph F. Goldberg, MD

11:30 AM
Combination Therapy in Bipolar Disorder
Nassir Ghaemi, MD, MPH

11:45 AM
Postsession Survey and Audience Q&A
Moderator: Roger McIntyre, MD
Panelists: Melissa DelBello, MD, MS; Nassir Ghaemi, MD, MPH; and Joseph F. Goldberg, MD

12:05 PM Non-CME Symposia

PSYCHEDELICS AND CANNABIS IN PSYCHIATRY
Moderator: Sidney Zisook, MD

1:30 PM
Presession Survey
Sidney Zisook, MD

1:45 PM
Impact of THC on Adolescents: Neurodevelopment
Christopher J. Hammond, MD, PhD

2:15 PM
Emerging Research for Cannabis Use Indications
Itai Danovitch, MD

2:35 PM
The Evidence for Psychedelics in Psychiatry
Rick Doblin, PhD

2:55 PM
Medical Crossfire®: How Useful Is Cannabis in Legitimate Psychiatry?
Moderator: Sidney Zisook, MD
Panelists: Itai Danovitch, MD; Rick Doblin, PhD; Christopher J. Hammond, MD, PhD

3:25 PM
Postsession Survey and Audience Q&A
Moderator: Sidney Zisook, MD
Panelists: Itai Danovitch, MD; Rick Doblin, PhD; Christopher J. Hammond, MD, PhD

3:45 PM BREAK

PSYCHIATRY IN SPECIAL POPULATIONS
Moderator: Anita Clayton, MD

4:15 PM
Presession Survey
Anita Clayton, MD

4:25 PM
Geriatric Psychiatry
Craig Nelson, MD

4:40 PM
LGBTQ+ Perspectives in Psychiatry
Jack Turban, MD, MHS

5:00 PM Cultural Challenges in Psychiatry (Immigrant Populations and Trauma, Going to Another Culture, etc.)
Richard L. Merkel Jr, MD

5:30 PM
Postsession Survey and Audience Q&A
Moderator: Anita Clayton, MD
Panelists: Richard L. Merkel Jr, MD; Craig Nelson, MD; and Jack Turban, MD, MHS

5:45 PM ADJOURN

NETWORKING RECEPTION
Saturday, October 2
8:00 AM Welcome and Opening Remarks
John J. Miller, MD

SPECIAL REPORT ON SUBSTANCE USE DISORDERS
Moderator: John J. Miller, MD

8:10 AM
Presession Survey
John J. Miller, MD

8:15 AM
Treatment for Opioid Use Disorder
Edward V. Nunes, MD

8:45 AM
Medication Treatment and Psychotherapy for Substance Use Disorders
Carla Marienfeld, MD

9:05 AM
Stimulant Use Disorders and Treatment Options
Steven Shoptaw, PhD

9:25 AM
Postsession Survey and Audience Q&A
Moderator: John J. Miller, MD
Panelists: Carla Marienfeld, MD; Edward V. Nunes, MD; and Steven Shoptaw, PhD

9:35 AM BREAK

SPECIAL REPORT ON SCHIZOPHRENIA
Moderator: Sanjai Rao, MD

10:05 AM
Presession Survey
Sanjai Rao, MD

10:10 AM
Diagnosing and Treating Schizophrenia
Christoph U. Correll, MD

10:45 AM
Long-Acting Injectables for Schizophrenia
Sanjai Rao, MD

11:10 AM
Advances in Predicting and Treating Tardive Dyskinesia
John J. Miller, MD

11:30 AM
Postsession Survey and Audience Q&A
Moderator: Sanjai Rao, MD
Panelists: Christoph U. Correll, MD; John J. Miller, MD

11:40 AM Non-CME Symposia

PERSONALITY DISORDERS
Moderator: John J. Miller, MD

1:10 PM
Presession Survey
John J. Miller, MD

1:20 PM
Adverse Childhood Events
J. Eric Vance, MD

1:40 PM
Differentiating Personality Disorders From Axis I Diagnoses
Mark Zimmerman, MD

2:10 PM
Borderline Personality Disorder
Carl Fleisher, MD

2:50 PM
Postsession Survey and Audience Q&A
Moderator: John J. Miller, MD
Panelists: Carl Fleisher, MD; James Knoll, MD; and Steven Shoptaw, PhD

3:10 PM BREAK

HOT TOPICS: WOMEN’S HEALTH
Moderator: Anita Clayton, MD

3:40 PM
Presession Survey
Anita Clayton, MD

3:50 PM Impact of Antidepressants in Pregnancy
Gail Erick Robinson, MD, DPsych, FRCPsych

4:20 PM Substance Abuse Treatment: Addressing the Specific Needs of Women
Jennifer L. Payne, MD

4:40 PM
Postsession Survey and Audience Q&A
Moderator: Anita Clayton, MD
Panelists: Jennifer L. Payne, MD; and Gail Erick Robinson, MD, CM, FRCPsych, OOnt

FUTURE OF PSYCHIATRY
Moderator: John J. Miller, MD

5:00 PM
Presession Survey
John J. Miller, MD

5:10 PM Technology: Software, Apps, and Wearable Devices
Jacob Behrens, MD

5:25 PM Emerging Pharmacologic Therapies
John J. Miller, MD

5:40 PM Neurostimulation: The State of Transcranial Magnetic Stimulation
Linda L. Carpenter, MD

5:55 PM Postsession Survey and Audience Q&A
Moderator: John J. Miller, MD
Panelists: Jacob Behrens, MD; and Linda L. Carpenter, MD

6:15 PM ADJOURN

To learn more and to register, visit event.gotoper.com/psych2021
ho doesn’t love summer? The days are longer and more carefree. This year, there is also a resurgence of energy and hope as many people begin to gather with family and friends, travel, visit a baseball stadium, and even send their children off to summer camp—all of which were missed last year with COVID-19 throwing a wet blanket over many traditional summer pastimes.

The field of psychiatry has held an important and unique role during the pandemic, in monitoring and addressing the mental health sequelae of isolation, quarantining, and grief, as well as the neuropsychiatric issues associated with the virus. Although many people feel they have cleared one of the last hurdles of this marathon, some folks have not been so fortunate. This month we feature 2 articles looking at the consequences of long-haul COVID-19 or postacute sequelae of SARS-CoV-2 infection (PASC). Elizabeth LaSalvia, MD, Jason Maley, MD, and Matcheri Keshavan, MD, share their insights from working on the front lines at Beth Israel Deaconess Medical Center. Psychiatrists and clinician like them are just beginning to understand the long-term consequences of this syndrome, including how to recognize it, how to treat it, and its prognosis. Similarly, Macy Bayern, MS, brings us into the world of 3 patients dealing with the neuropsychiatric sequela of COVID-19, serving as a reminder of the continued challenges presented by the virus, even as new infection rates continue to drop.

Fortunately, medicine and psychiatry continue to rally. In February, the National Institutes of Health launched an initiative to further study long COVID and, just as this issue was going to press, NYU Langone Health announced that it was selected as the clinical science core. An interdisciplinary team will lead the investigation as multiple diverse patient groups are followed over time to track symptoms in hopes of better understanding treatment issues and the underlying mechanisms of PASC.

Nonetheless, we remain resilient in the face of this ongoing crisis; indeed, the focus of this month’s Special Report is resiliency. Editorial Board member Phebe Tucker, MD, leads the charge in exploring this understudied area of psychiatry. In addressing the nurture versus nature debate, Ping member Phebe Tucker, MD, leads the charge in exploring this understudied treatment issues and the underlying mechanisms of PASC.
FROM THE EDITOR

Perfecting the Trifecta

John J. Miller, MD | Editor in Chief

Imagine practicing medicine in the early 1900s before the advent of antibiotics, anesthesia, laboratory data, radiology, and intensive care units. Clinicians did not need to know as much as we do today. Of course, that also meant there was less we could do for our patients. I can recall as a child during the 1960s my grandmother was hospitalized for a week for a headache—and the prescribed treatment was rest.

Fortunately, we continue to expand our understanding in all medical specialties at an exponential rate. Add to that the extraordinary demands of clinical practice, and at the end of our workday, we simply do not have the energy to read an onerously written article in a medical journal. Not surprisingly, this void has been filled by medical conferences, where the goal is to focus on learning all that is new and important in our chosen field of medicine. These conferences are often enriched by reunions with our longtime friends and colleagues as well as by spending a few extra days vacationing away from our usual routines. This combination of events likely enhances retention of the material learned and provides a well-needed respite from our daily medical practices.

In the attempt to keep mental health professionals up-to-date, the mission of Psychiatric Times™ since 1985 has been to provide evidence-based, peer-reviewed, clinically relevant information for psychiatry. More than 200 leading topic experts, the conference provides a rich, diverse curriculum that is designed to reward attendees with a meaningful and broad educational experience. Plus, the CME credits earned are a pleasant value-added perk.

The Annual Psychiatric Times™ World Conference will be held September 30 through October 2. Building on last year’s successful virtual conference, we are excited to offer a hybrid conference model that allows attendees to participate in-person—in San Diego, California—or virtually, with both formats providing access to the same great information and same outstanding faculty. In addition to updates on the usual topics like psychotic disorders, affective disorders, and substance use disorders, presenters will share their experiences and insights on numerous specialty topics.

This year’s conference will begin with a mini-symposium on “Psychiatry in the Age of COVID-19,” exploring how our lives changed during this once-in-a-century pandemic, and how this experience has changed the way we practice psychiatry, grieve from a global disaster, and heal from the physical and mental scars left behind.

Needless to say, the past 18 months have been extraordinary in...
Let’s Use the Pandemic to Change Health Care for the Better

L. Allen Dobson Jr, MD, FAAFP

The COVID-19 pandemic should have us reflecting on the state of our health care system as well as embarking in a national dialogue on what type of system we want for this country and what investments we need to attain that vision.

So many questions arise when considering the pandemic: Why were we so ill prepared to mount a national response? Why are health care costs so high? Why does so much of the population have such poor access to basic care, with racial and economic disparities so pronounced? What should be our focus going forward? Here are a few thoughts about telemedicine. One thing seems clear: A hybrid model will likely become the “new normal” in health care delivery.

Many other lessons have been learned—like the importance of self-care for clinicians and caregivers—and hopes for improvement abound as we venture forth. As many have said, returning to normal should not be the goal: We should aim to better incorporate the successful innovations gleaned from the pandemic into our routines.

In addition, the COVID-19 pandemic remains unleashed in many countries, and although vaccination rates in the United States continue to rise, most of us still feel off-balance because of the raw experiences of the past 18 months. There is much to feel, discuss, share, and process about this viral pandemic, and this symposium’s sessions will explore all of that, as well as the psychiatric implications of COVID-19.

In another vein, the conference will feature a series of presentations examining what we know about cannabis, tetrahydrocannabinol, and cannabidiol, a timely focus with cannabidiol legal—both medically and recreationally—in a rapidly growing number of states. In the not-so-distant future, it could be legalized throughout the United States. Similarly, psychedelics, which had been marginalized since the 1960s, have resurfaced with possible benefits for some psychiatric disorders. For instance, more than 50 clinical trials are currently registered with the US Food and Drug Administration researching the putative benefits of psilocybin for various indications.

How might psychedelics become a novel psychiatric treatment in our toolbox? The conference will explore new research and what you need to know.

So many more equally fascinating talks are scheduled. In partnership with Physicians’ Education Resource® (PER®), we are continuing our conference model of presenting many diverse topics in brief time intervals to allow for a broad curriculum, providing you with key take-home points in a clear and focused manner. I invite you to review our entire conference schedule online at https://bit.ly/3fXHeH1 and consider registering to attend either in person or virtually.

My favorite part of our annual conference is the ample time for faculty interaction with attendees to discuss cases or delve deeper into topics of interest. For participants attending in person, please join us for a networking reception on the evening of Friday October 1. If you have previously visited San Diego, you already know why it is such a special city. If you haven’t, it is time to find out.

I look forward to seeing you there—and learning together!
COVID-19 Mental Health Long Haulers

Continued from Cover

“I live in terror that I’m going to kill my mother,” Sims said. “That’s my biggest fear: I’m going to bring COVID home to her.”

At the Arkansas Industrial Traffic Association, Sims manages the company’s finances in person for security reasons. Seven individuals work in the office, and masks are not required at their desks, which scares her.

Sims’s concerns are widely shared. Between April and June of 2019, nearly 11% of Americans experienced anxiety and/or depression, according to the National Center for Health Statistics National Health Interview Survey. However, during the same time frame in 2020, when COVID-19 began overwhelming the United States, the Centers for Disease Control and Prevention’s Household Pulse Survey found that 35.6% of Americans reported symptoms of anxiety and/or depression.

“Long haulers,” a recently popularized term, are individuals experiencing long-term symptoms of COVID-19. Now, after more than a year of COVID-19 in the United States, doctors show that long haulers continue to experience both physical and mental symptoms.

The definition of mental long haulers, especially those with mental health issues, is still developing. Syed Iqbal, MD, a psychiatrist and assistant professor at Baylor College of Medicine, told Psychiatric Times that although he believes that COVID-19 can cause long-term mental health problems, he is awaiting further longitudinal data for proof. Some confirmatory evidence has come in the form of study results published in The Lancet Psychiatry, finding that 1 in 3 patients who recovered from COVID-19 later developed neurological or psychiatric conditions within 6 months of infection, with anxiety and depression topping the list.

From Nervousness to Mental Health Disorder

What is really happening with these patients? To find out, Psychiatric Times followed 3 women—Dawn Sims, Heather Scott, and Lisa Germain—from November 2020 to February 2021, the time frame of the pandemic’s second US surge. Although three women is a small sample size, the impact of COVID-19 on these individuals’ mental states was massive. Their 3 stories were very different yet shared certain commonalities.

Mainly, they shared a common distress about the persistent anxiety. In December 2020, that concern overwhelmed Sims. “I am 100% certain that I am going to get it, and I am 100% certain that I’m going to give it to my mother,” she expressed.

From the time Sims was young, she was “a worrier,” but COVID-19 exacerbated her tendencies. “I’m having full-fledged panic attacks,” Sims said. “It’s gone from just being a nervous person, to this.”

Heather Scott, aged 47 years, of Pinconning, Michigan felt the same way as Sims, except her anxiety started when she contracted COVID-19 in November 2020. Two months after her diagnosis and 1 month after her physical symptoms ceased, Scott remained bedridden with depression and anxiety.

“When I was not asleep, Sims was online reading about other individuals’ lasting symptoms. All 3 women belong to a coronavirus emotional support group on Facebook. They said they joined the group to vent and share experiences, but they agreed the comments and information shared in the group sometimes make them feel worse.

A study published in August 2020 in Computers in Human Behavior Journal featured survey results looking at social media’s impact on mental health during the pandemic in residents of Wuhan, China. Investigators found that social media initially provided peer support, but increased exposure to COVID-19–related materials resulted in higher levels of depression.

On Scott’s good days, the group helped her feel less alone. Still, her physical isolation from others overwhelmed her, and she sought help from a psychiatrist.

A Silver Lining: Resilience During COVID-19

All 3 women had not received any therapy before COVID-19. Alana Mendelsohn, MD, PhD, a psychiatrist resident at the Columbia University Medical Center, noted that patients with whom she had seen prior to COVID-19 were better able to handle COVID-19–related stress.

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“The patients would say, ‘I’ve already been in therapy, working on these issues, developing the skills,’” Mendelsohn explained to Psychiatric Times. Through previous therapy, these patients had increased their mental resilience and acquired the necessary tools to better cope with COVID-19’s uncertainty and chaos.

Individuals who had not been in therapy prior to COVID-19 tend to struggle more, Mendelsohn said. Even individuals who did not previously need mental health care have developed pandemic-induced mental disorders.

Study findings published in the December 2020 Journal of Affective Disorders showed that participants with higher mental resilience experienced less mental distress during the pandemic, although those with lower resilience had more difficulty coping.1

“As we learned from 9/11 and [superstorm] Sandy, some people are resilient, but not everybody is,” Sederer explained. As the mental hygiene commissioner for New York City, he led the mental health–related responses to the events of September 11, 2001, to superstorm Sandy, and to other disasters.

Factors that predict lower resilience include “having a previous mental health or addiction problem,” said Sederer. “The people most predictive to get sick again were the ones who were sick before.”

“The mental health consequences of [the pandemic] are going to be with us for a very long time, unfortunately,” Mendelsohn added.

That very sentiment is Scott, Germain, and Sims’ biggest fear.

Looking to the Future
Sitting in her Florida home with self-described “anxiety knots” in her stomach, Germain yearned to feel like she can care for herself. She reported her anxiety was still “so freakin’ high.” Scott still gravitated to her bedroom in Michigan, as her mental health issues persisted. “The mental [part] is the worst part of it all. It’s debilitating,” she said.

Sims fully recovered from COVID-19’s physical symptoms, but she did not recover from her heightened anxiety. “I’ll always feel like there’s potential that someone is carrying a disease that could spread,” she said.

She still keeps her mother at a distance.

Ms Bayern recently earned her degree from the Columbia Journalism School in New York, New York. Previously, she was an associate staff writer at TechRepublic.

REFERENCES

Developing a Collaborative Approach to Post-Acute Sequelae of SARS-CoV-2 Infection

Continued from Cover

The effects of COVID-19 are expected to last for a long time, with evidence for persistent and/or delayed significant symptoms beyond 4 weeks from the onset of acute illness.1 It has been observed that as many as three-fourths of patients hospitalized with COVID-19 had at least 1 ongoing symptom 6 months after acute illness,2 and 30% of patients, even those with mild illness, have reported persistent symptoms for as long as 9 months.3 These long-term consequences include mental health issues, with 1 in 3 COVID-19 survivors having persistent neurological and/or psychiatric consequences.2

This recognized phase of prolonged illness, referred to by a variety of names including long COVID-19, long-haul COVID-19, and postacute COVID-19, has been recently designated by the National Institutes of Health as post-acute sequelae of SARS-CoV-2 infection (PASC).3

The Multifactorial Consequences of PASC
Although COVID-19 had initially been most notorious for causing respiratory pathology, with the most vulnerable patients progressing to acute respiratory failure, its extrapulmonary manifestations are now known to be prominent.1,4 PASC is viewed as a multisystem disease with an underlying etiology still to be determined but possibly involving dysregulated immune response, inflammation, microvascular thrombosis, and/or cellular damage from the virus.4 Although variable in presentation, PASC most commonly involves a constellation of symptoms (Table).5 The symptoms of PASC range from mild to disabling with significant effects on quality of life, even in patients whose acute course of illness was mild or who were previously healthy and active.4,11

We have much to learn about PASC, due to the multiorgan system effects and the heterogeneity of symptoms in patients who survived COVID-19. Beth Israel Deaconess Medical Center, a patient care, teaching, and research affiliate of Harvard Medical School in Boston, has recently launched the Critical Illness and COVID-19 Survivorship Program. The program aims to integrate care among pulmonary, critical care, sleep medicine, psychiatry, cognitive neurology, neurology, geriatrics, social work, and physical and occupational therapy clinicians. Although the cases differ, 3 deidentified vignettes demonstrate the core themes for patients presenting with PASC who are referred
The Mental Health Impacts of ICU Admissions

Prior to the COVID-19 pandemic, it had been increasingly recognized that survivors of ICU admissions commonly experience long-term physical, psychological, and cognitive impairments that adversely impact their quality of life. This group of multisystem impairments is referred to as post-intensive care syndrome (PICS). More than 50% of survivors of acute respiratory syndrome suffer from at least 1 feature of PICS a year after their ICU stay. More specifically, depression, anxiety, and PTSD are well characterized and persistent manifestations of PICS. The differences in characterization and etiologies between PICS and the independent influence of COVID-19 is not yet understood.

VIGNETTE 1

“Alma,” a woman aged 45 years, presents with a history of hypertension and a 4-week intensive care unit (ICU) stay due to acute respiratory failure, prolonged intubation, and paralysis after contracting COVID-19. Alma’s ICU stay was complicated by a course of delirium. She had been discharged home from a rehabilitation center more than 6 months prior to her appointment. She has been referred for ongoing symptoms of posttraumatic stress disorder (PTSD) related to her ICU stay, significantly impaired sleep, and depressed mood. Additionally, Alma continues to struggle with ongoing memory and focus concerns, shortness of breath, and difficulty with weakness. Her cognitive and physical symptoms have improved, but they remain impairing.

VIGNETTE 2

After contracting COVID-19, “John,” a man aged 70 years with a history of asthma, obstructive sleep apnea, diabetes, and major depression, was hospitalized for 4 days due to low oxygen levels, which required treatment with steroids. John presents 3 months after hospitalization with worsening depression, insomnia, breathlessness, and related anxiety. His mood is also influenced by frustration with obstacles in restarting home health services. Due to a lack of assistance, it has been difficult for John to keep up with his many follow-up appointments or go to the pharmacy to pick up medications and other medical supplies. He reports being quite lonely and has not seen his out-of-state family for many months.

VIGNETTE 3

“Susan” is a woman, aged 40 years, with a prior episode of major depression that had been in remission and mild attention-deficit symptoms that had been well controlled. She presents more than 7 months after contracting COVID-19. During her acute course, she struggled with fever, cough, headache, shortness of breath, fatigue, and anosmia. Susan was evaluated in the emergency department due to the severity of her symptoms, but she did not require hospitalization. She has had persistent symptoms of breathlessness, profound fatigue, difficulty with concentration and memory, insomnia, and difficulty performing the duties of her job, which she has held for many years. She is referred for growing depression and feelings of hopelessness.

Symptoms of Lower Severity, but High Persistence

This clinical presentation—a patient who is younger, previously healthy, with milder acute COVID-19 symptoms and persistently impairing symptoms longitudinally—is often referred to as long COVID-19. Earlier in the pandemic, this clinical presentation was not fully recognized and, indeed, sometimes ignored or discounted. Long COVID-19 challenges clinicians more than ever to listen to patients and break down the false dichotomy between mental and physical health. The experience of feeling trivialized and frustrated by an overemphasis on the psychological components of illness has been shared by survivors of prior coronavirus epidemics such as severe acute respiratory syndrome (SARS) in early 2000s and Middle East Respiratory Syndrome in 2012. It also has been a common experience in patients diagnosed with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), a complex and disabling illness with features that overlap those of long COVID-19.

The presentation of neuropsychiatric symptoms after COVID-19 are heterogeneous, and to some extent they may reflect variable and multifactorial causes. The either/or characterizations of symptoms by patients, clinicians, and society alike of psychiatric vs organic, psychological vs physiological, functional vs neurological, are all overly simplified and represent antiquated views of the brain-body connection. Breaking down long-standing silos in health care through the use of integrated multidisciplinary teams will be critical to finding more effective treatments. Bridging this divide is urgent, not only to understand and treat the consequences of this pandemic, but also to face the longstanding issue of mental health stigmatization that serves as an enduring barrier to patients seeking care for their mental health. Patients with PASC are at risk of mental health consequences, whether it be from the direct consequences of the virus, indirect consequences of quarantine and the pandemic, exacerbation of preexisting conditions, or/and ongoing challenges of coping with a new, poorly understood, chronic illness.

Issues to Consider in Treatment and Recovery

Many patients slowly recover with supportive measures and symptomatic treatment. Much of the initial recovery recommendations focus on physi-
Dr LaSalvia is a geriatric psychiatrist at Beth Israel Deaconess Medical Center (BIDMC) and an instructor at Harvard Medical School. She is the consulting psychiatrist for the BIDMC Critical Illness and COVID-19 Survivorship Program. Dr Maley is a pulmonologist and critical care physician at Beth Israel Deaconess Medical Center and a researcher at Harvard Medical School and the Massachusetts Institute of Technology. He directs the BIDMC Critical Illness and COVID-19 Survivorship Program. Dr Keshavan is Stanford Cobbs Professor and Academic Head of Psychiatry at Beth Israel Medical Center and Harvard Medical School.

REFERENCES


Two Crises I Didn’t Train For

Richard Berlin, MD

Telepsychiatry makes it easier for psychiatrists to treat patients by eliminating the need for either party to travel, with services provided from the safety and comfort of the psychiatrist’s home.

- Telepsych website

I can still hear my patient's voice when a black bear appeared on camera behind me, circled the rose garden sundial, and reared up to study one small human shielded only by a sunroom screen, three hundred feral pounds of muscle and claw, almost as frightening as a virus a tenth of a micron wide.

Dr Berlin has been writing a poem about his experience of being a doctor every month for the past 23 years in Psychiatric Times, in a column called "Poetry of the Times." He is instructor in psychiatry, University of Massachusetts Medical School, Worcester, Massachusetts. [1]


In our psychiatric practices, we naturally focus on psychopathology and the negative effects that adverse and traumatic experiences have on our patients’ mental health. We assess disaster survivors’ maladjustment in order to develop policies for mental health recovery programs. However, the majority of individuals exposed to disasters or other traumatic events do not develop posttraumatic stress disorder (PTSD) or another lasting psychiatric disorder, although they may experience temporary ripples on the surface of their emotional lives and subclinical symptoms for a time.

In considering the patients seen by my residents and me, I am often in awe of the tremendous strength that many of them have developed despite experiencing horrific abuse, neglect, disasters, extreme poverty, major losses, and other traumatic events. Some who were severely abused or neglected as children become devoted parents or highly functional adults, albeit with effort. How do we understand this emotional hardiness?

Resilience is a relatively neglected research topic. A Medline search for medical literature related to “psychological resilience” revealed only 6471 articles, whereas a search for articles related to “PTSD” and “posttraumatic stress” (which does not include other mental health problems associated with trauma) identified 36,682 and 18,823, respectively. In fact, in my own research on biological markers for symptoms and diagnoses of PTSD, depression, and anxiety after disaster, we explored heart rate and blood pressure responses, heart rate vulnerability, and levels of cortisol, interleukin-2, and interleukin-6—yet we did not explore those markers or personal characteristics associated with resilience.

Part of the problem is that resilience is difficult to define. Is it the absence of mental health diagnosis, or is it having temporary symptoms or symptom levels below a defined threshold of distress? Or is it having a fulfilled life and pursuing cherished life goals?

However we define resilience, what factors contribute to it? Are some individuals blessed with a fortunate genetic endowment or temperament? Some research has shown heritability of resilience to range between 33% and 52%. Research on resilience has implicated genetic variations in expression of neuropeptide Y and regulation of the HPA axis, as well as polymorphisms in noradrenergic and dopaminergic systems and serotonin transporter genes. Conversely, epigenetic factors involve methylation, demethylation, and histone changes after stress, especially early life stress, which can change gene expression but not DNA structure, for a variable amount of time, contributing to psychiatric vulnerability. Does this “hop on, hop off” epigenetic model for stress response inversely explain emotional hardness? Recent research results point to an association between maternal resilience and increased cellular telomere length in newborns, with longer telomeres important in gene transcription, meiosis, and cellular longevity. Can promoting maternal adaptation to stress during pregnancy have protective factors in offspring? Other biological differences associated with positive or negative adjustment after emotional stressors include, but are by no means limited to, hippocampal volume, HPA axis reactivity, the mesolimbic dopamine pathway, and differences in inflammatory markers such as neuropeptide Y, cytokines, and C-reactive protein—before or after trauma exposure.

Experience is also important in resilience. Would stress inoculation in developmental years—having just enough but not too much exposure to hardship-enable individuals to overcome lifetime adversity? This concept...
has been noted in different cultures—for example, an African proverb intones, “Smooth seas do not make skillful sailors,” and William Shakespeare wrote, “Sweet are the uses of adversity,” in As You Like It. Moreover, as children learn to face inevitable life challenges, having love and support from parent figures or mentors can be protective.

Other factors have been associated with emotional buoyancy: using active coping mechanisms, cognitive reappraisal of negative thoughts, physical exercise, mindfulness, and meditation. Having sufficient social support, higher socioeconomic status, and higher educational levels also protect individuals’ psyches. Thoughtful creators of everything from ancient religious and philosophical texts to modern neurobiological and psychological research have linked resilience and life satisfaction with the wisdom that can come with aging. Thus, wisdom, resilience, and better health are promoted by the sharing of life experience lessons from older to younger generations.

Drawing on the tenets of psychoanalysis, some experts have recommended the use of mature ego defenses, such as creativity, humor, and altruism, in the face of difficulty. Humor and altruism have the particular benefit of drawing others in, thus increasing social support.1

Relevant to our current pandemic, the results of a recent large study of frontline health care workers caring for hospitalized COVID-19 patients linked psychological resilience with positive emotions, self-efficacy, sense of purpose in life, and social support (including leadership support), as well as with avoidance of maladaptive behaviors, such as substance abuse.4

In sum, resilience is a rich but understudied field for psychiatric research. In this Special Report, we are honored to present several expert colleagues’ wisdom on psychiatric resilience in diverse areas.

Dr. Tucker is vice chair of education for psychiatry and behavioral sciences, holds the Professor and Arnold and Bess Ungerman Endowed Chair in Psychiatry and the Robert Glenn Rapp Foundation Presidential Professorship of Psychiatry, and serves in the Adult Mental Health Services at the University of Oklahoma College of Medicine, Oklahoma City.

REFERENCES

Exploring Resilience

Resiliency and Posttraumatic Growth: Cultural Implications for Psychiatrists

Ping Zheng, MD, PhD; Andreas Maercker, MD, PhD

Resilience is a common term that describes individuals’ amazing capacity for resistance. Its sibling term, posttraumatic growth (PTG), is less well known, however. PTG describes the positive psychological changes individuals will be able to notice in themselves in spite of a traumatic experience. Examples of PTG include statements such as, “Despite all the bad things that happened, I realize that I feel much more connected to other people now,” or “After what happened, I find myself focusing more on what is important to me and not what others want me to do.”

The resiliency concept has had many academic mothers and fathers, including Emmy Werner, PhD, (1929-2017; developmental psychologist at the University of California), and George Vaillant, MD, (born 1934; psychiatrist at Harvard University). The concept of PTG derives substantially from the work of psychologists Lawrence G. Calhoun, PhD, and Richard G. Tedeschi, PhD, from the University of North Carolina. Their cutting-edge research drew inspiration from ancient sources, including Greece and the Judeo-Christian Bible, as well as some of the teachings of Hinduism, Buddhism, and Islam that contain statements on the possibility of positive change through one’s own suffering.1

Over the past 20 years, the main area of application for PTG and resiliency research has remained posttraumatic stress disorder (PTSD). As this disorder is globally prevalent and one that affects many US immigrants, it is important to assess the relevance of these concepts in a global context, especially for individuals from socially disadvantaged countries. Also important is that comorbidities are common in many patients with psychiatric disorders. Therefore, the area of application of PTG and resiliency research has expanded to include more mental disorders.

A significant question that has arisen from global research on the topic remains: How much resilience and PTG can humans draw from themselves?2

PTG, Positive Psychiatry, and Resiliency

PTG has been reported in individuals who have experienced sudden loss of a loved one, chronic life-threatening medical conditions (eg, cancer, HIV infection), infectious diseases (eg, COVID-19), sexual assault/abuse, or refugee experiences.3 PTG may exist with distress in the context of suffering and significant psychological struggles. The changes associated with PTG are experiential and powerful, encouraging survivors of adversity to spend time altering their cognition of the world and the self. Resiliency is the trait-like capability of maintaining normal psychological functioning in the face of adversities or challenging life conditions. It is associated with the ability to interact flexibly with the environment and use personal resources effectively. Resiliency is relatively stable but not static because this capability may grow through cognitively recon-
Cultural Understanding of Psychiatric Resilience

Culture is a social constellation of components that include practices, competencies, ideas, symbols, values, norms, institutions, goals, constitutive rules, artifacts, and modifications of the physical environment. In clinical settings, culture involves contextual features, such as the economics, availability, and accessibility of services; patient variables, including differences in prevalence or manifestation of disorders, preference of alternative treatments, health literacy, and adherence; and provider variables, such as referral bias and patient-clinician alliance. Cultural differences in clinical representations of mental disorders have been evident in key domains of social and occupational functioning for psychiatric patients in the United States, Denmark, the United Kingdom, Norway, and Israel.19

Experience positive changes in the aftermath of their adverse experiences, higher levels of resiliency are nonetheless associated with higher levels of persistence and self-directedness in patients with chronic psychiatric illness.16 According to the Cloninger model, both environment (ie, character dimensions) and genetic endowment (ie, temperament dimensions) contribute to resiliency.20

Cultural factors may affect resiliency through genetics and environment. In terms of genetic factors, culture may contribute to, or interact with, individuals’ self-identifying process through biological characteristics (eg, skin color, eye color, or facial features associated with race), behavioral phenotype (eg, eye movement deficits in schizophrenia), and the way they perceive adversities related to psychiatric disorders.21

Environmentally, culture may shape resiliency by influencing human developmental processes and behavioral patterns through religion, education, and other physical circumstances. Research indicates that culture may moderate the relation between adversity and psychiatric disorders such as PTSD.21

As one of the most important components of culture, religion may affect one’s comprehension of the world and the self. Table 1. Religious contexts and spiritual appraisals of traumatic events have a robust relationship with posttraumatic outcomes, including PPTG. The trauma recovery process involves rebuilding an assumptive world. Religion provides a meaning-making framework to process traumatic experiences and its related distress, as has been evidenced by different cultural studies. For example, results of a study of Kashmiri children demonstrating PPTG after experiencing a traumatic event indicated that religion had a positive effect on their coping.22 Many Asian cultures are not anchored in one particular religion; instead, spirituality in such cultures might be better understood from an existential perspective. Thus, spirituality may be represented in a manner related to resilient behavior and infused within a general approach to life in those cultures.

“When we as professionals acknowledge patients’ ability to recover and grow, they feel more understood despite their often ongoing state of suffering.”

The Measuring and Implications of Resiliency

Preventive psychiatry aims to promote health and to protect individuals from developing mental disorders through early diagnosis, effective treatment, disability limitation, and rehabilitation. Preventive assessment and intervention have found to be reduced symptoms in some mental illnesses, including depression, psychosis, anxiety, and conduct disorders.23 The use of positive psychosocial intervention in children and adolescents to alleviate possible negative outcomes is part of the resiliency-enhancing process.

When we as professionals acknowledge patients’ ability to recover and grow, they feel more understood despite their often ongoing state of suffering. Interventions involving resiliency-enhancing and PPTG-recognizing processes may benefit not only patients, but also health care workers and caregivers.
Resilience and Healthy Aging

Igor Linkov, PhD, MSc; Stephanie Galaitsi, MSEE; Katarzyna Klasa, MPH, BSN; and Andrew Wister, PhD

In psychiatry and psychology, resilience is identified as an individual’s positive adaptation to life tasks under stressful and adverse social situations, or positive growth that mediates rates of recovery after disruptions.1,2 The concept describes dynamic coping capacity related to risk factors (eg, stressful life events such as disease, loss of social support, financial hardship).3 Psychological resilience can be influenced by the interaction of internal factors (eg, cognitive capacity, personality, physical health) and external resources (eg, social status, financial stability).4,5 These can be leveraged—along with biological, psychological, social, and environmental protective and promotive factors—to shift an individual along the path from adversity and disruption to adaptation, recovery, wellness, and even growth.6,7

We define “resilience” as the ability to recover from disruptions, in contrast to either preventing disruptions or allowing them to be deterministic.8 This definition is consistent with the National Academies of Science (NAS) definition of resilience in the face of natural disasters,9 a framework that can be applied to resilience for aging adults with applications to psychiatry.10 The critical functions for aging adults in a resilience analysis might include the ability to live independently, or to engage meaningfully in certain activities. In a psychiatric context, these critical functions can be defined by both patients and clinicians, rather than only by researchers who may not fully capture what individuals deem important.11 For psychiatric health in older adults, resilience includes acceptance that adversity and disruption to adaptation, recovery, wellness, and even growth depend.12

Aspects of Resilience

Resilience, as envisioned by the NAS, is composed of 4 separate phases: preparing for a disruption, absorbing a disruption by decreasing certain critical functions (such as rationing food, water, energy, and communication during a disaster), recovering, and finally, if possible, adaptation to improve critical functions. For older adults, these phases occur within an expected decline due to the normal aging process, and resilience theory aims at recovery that fits a patient’s specific aging trajectory. A patient’s decline can be accelerated by disruptions such as the death of a partner, serious accident, or a pandemic.12

Among aging individuals, mental health and illness adversity may be long-term chronic, episodic, or acute, and it may require consideration of the life course. For instance, some individuals struggle with depression or bipolar disorder over many years, whereas others may face life crises, such as dementia or suicidal ideation, that arise during later life. Additionally, we can identify 2 contrasting generic resilience and aging trajectories: (1) declines in physiological and psychological resilience due to normal aging; and (2) increases in resilience due to social learning and successful coping strategies. The unique contexts of aging are incorporated into the resilience process (Figure 1).12

The resilience matrix, originally conceived by Linkov et al12 and based on system capabilities from Alberts and Hays,14 can be applied to an individual (in conjunction with a clinician) to help develop their psychiatric resilience. The resilience matrix emphasizes 4 domains of critical functions that can help a patient identify and articulate aspirations and interventions within a resilience context (Figure 2).13,14 In the case of psychiatric evaluation, the domains also could be characterized in 4 ways (Table).

Building Resilience Together

To apply these components of psychiatric resilience and aging, the clinician will need to work with each individual patient to determine the critical function(s) most important for their recovery. Such critical components might include identity and self-image development to enhance meaning in life, relationships with family members, and the ability and desire to live independently. Clinicians can structure resilience-oriented treatment using the aforementioned matrix to prioritize critical functions before or during disruptions in order to manage the absorption, recovery, and adaptation process.

For clinicians to operationalize the resilience matrix, they must differentiate resilience-by-design and resilience-by-intervention.15 The former assumes that a system can internally reconfigure to adjust and recover following a disruption, while the latter relies on external resources.

In the case of clinicians, this resilience matrix can help frame the external support (resilience-by-intervention) that a clinician might offer their patients. In addition to supporting patients after disruptions, the resilience matrix framework can provide avenues for patients to build internal resilience (resilience-by-design) for the future, or to mobilize existing internal resilience. A clinician focused on a particular patient can tailor resilience strategies that capitalize on the patient’s unique strengths and circumstances, which for older adults, compared with young individuals, include considerable experiential contexts and learning. Similar to designing resilient systems in engineering, psychiatrists can develop strategies to enhance individuals’ mental health. Ensuring overall mental health through the use of relevant medications and treatments approximates resilience-by-intervention in broader governance (like stockpiling resources in the case of crises).

Disruptions can take many forms for patients, and a resilience-oriented treatment plan is not predicated on predicting which disruptions will arise. For clinicians, the preparation phase should establish a relationship with the patient that is characterized by trust. This relationship, and other preparation areas that can be identified in collaboration with the patient, constitute a suite of potential resilience systems that can be leveraged and enhanced before a disruption occurs. Protective factors might include a propensity to set conditions for rest, meditation, relaxation, restoration, and social engagement; development of mastery and self-confidence; practicing positive behaviors such as cultivating and maintaining loving, supportive

<table>
<thead>
<tr>
<th>CRITICAL FUNCTION</th>
<th>TIME</th>
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NAS DISASTER RESILIENCE

PLAN → ABSORB → RECOVER → ADAPT

PSYCHIATRIC RESILIENCE IN AGING

PLAN → ABSORB → RECOVER → ADAPT

Table. Four Domains of Resilience

<table>
<thead>
<tr>
<th>Domain</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Physical</td>
<td>Physical integrity of body; continued use and/or enhancement of mental faculties</td>
</tr>
<tr>
<td>Informational</td>
<td>Exposure to, collecting, and processing information; challenging oneself to learn and employ new information</td>
</tr>
<tr>
<td>Cognitive</td>
<td>Emotional regulation and reintegration; decision models that acknowledge uncertainty, including engagement with biases and values. Focus is on use of the information and physical domains to make decisions</td>
</tr>
<tr>
<td>Social</td>
<td>Ability to interact, collaborate, and connect to other individuals; role maintenance; prosocial behaviors like empathy</td>
</tr>
</tbody>
</table>

Figure 1. Resilience, Aging, and Disaster Response

Figure 2. Resilience Matrix
relationships; and problem-solving ability. These constitute a patient’s resilience-by-design; meaning the internally embedded perspectives, learned coping strategies, reflexes, and management strategies that enable patients to face crises productively as they arise.

Building a patient’s resilience-by-design in the preparation phase provides the patient with the appropriate tools or learned perspectives to apply when a disruption occurs, thereby initiating the absorption process. Absorption is the process of encountering the disruption and subsequent loss of critical function, which can vary in magnitude according to resilient resources available. Such resources include collaborative work with the clinician, who can evaluate the components of the resilience matrix and identify elements or skills that may need clinical direction. The clinician can help the patient identify when the switch is made from absorption to recovery and guide the patient to the tools best suited for each stage. These resilience-by-interventions rely on the clinician’s understanding of the patient’s needs and goals, and existing foundational resources, and the clinician’s ability to supplement any resources that are missing or depleted.

Finally, adaptation asks the patient to use the disruption as an opportunity to reevaluate and potentially change habits or behaviors that were either previously deficient or have become untenable under new circumstances. This phase of resilience invites the patient to reimagine ways to support their critical functions, which should either ensure the return to the patient’s original trajectory or, possibly, their return to an improved trajectory, if they have embraced the opportunity to evaluate and carefully optimize beliefs and behaviors.

**Concluding Thoughts**

This resilience matrix framework can be empowering to older adults. At a population and public health level, the coronavirus pandemic has revealed that older adults may be better positioned to cope with stressful situations, such as social isolation, than their younger counterparts. The reasons for this are numerous, and they likely include the confluence of more resources, previous learned experiences, and fewer responsibilities. Regardless of the reasons, the results of these studies provide a counterpoint to the idea that elderly patients are frail and helpless.

Ultimately, degradation to death remains an inevitability, but resilience can be part of the tool kit to prolong life and, equally important, to prolong the period when quality of life can be maximized. Some study results suggest that increasing psychiatric resilience could be comparable in importance with decreasing physical disability in terms of ensuring successful aging. A resilience framework, structured by the resilience matrix, can help clinicians support patients prior to and during disruptions to their lives, whether those disruptions are anticipated or not.

**Dr Linkov** is the senior science and technology manager of the US Army Engineer Research and Development Center (ERDC) and an adjunct professor at Carnegie Mellon University. He is responsible for ERDC’s project portfolio in the areas of crisis management and resilience. He has published widely on environmental and technology policy, and on risk and resilience analytics, including 25 books and more than 400 peer-reviewed papers and book chapters. Ms Galaitis works with the Risk and Decision Science team within the US Army Corps Engineer Research and Development Center. Her research topics include the public health response during the 2020-2021 coronavirus pandemic, government of synthetic biology, stakeholder engagement in water resource management, automated algorithms and artificial intelligence, and resilience applications in fields like gerontology, team behavior, and value chain analysis. Ms Klasa is a PhD candidate in health services organization and policy at the University of Michigan’s School of Public Health, Department of Health Management and Policy. She uses mixed methods to explore the intersection of health policy, risk/resilience, and politics, drawing from cross-disciplinary training in nursing, health care management, public health, economics, and political science. Dr Wister is director of the Gerontology Research Centre and a professor in the Department of Gerontology at Simon Fraser University. His work has been published often on topics such as baby boomer health dynamics; population aging and population health; resilience and aging; social isolation; and environmental adaptation among older adults. His most recent book, Resilience and Aging: Emerging Science and Future Possibilities, co-edited with Theodore D. Cosco, was published in 2021 by Springer.

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The Rise in Synthetic Cannabinoids and Cathinones

Sameer Hassamal, MD; and Sunita Hassamal, MD

The rise in synthetic cannabinoi
doid use has been linked to a wide range of unpredictable effects, including agitation, psychosis, and delirium. Managing and stabilizing the complex effects of these drugs can be challenging.

Synthetic Cannabinoids

Colloquially known as spice, these designer synthetic cannabinoid receptor agonists have potent intrinsic activity at the cannabinoid (CB1) and 2 receptors. The compounds were originally developed to study the endocannabinoid system, but they emerged as a drug of abuse in 2008. Initially designed to mimic the effects of 9-tetrahydrocannabinol, synthetic cannabinoids are 2 to 100 times more potent than marijuana at the CB1 and CB2 receptor, resulting in a range of adverse neuropsychiatric symptoms (Table 1). Furthermore, synthetic cannabinoids are often adulterated with ingredients to either enhance or attenuate the drug high, resulting in clinically unpredictable toxicological profiles. As a consequence, no specific toxidrome is associated with synthetic cannabinoid intoxication, and patients will typically present with a constellation of sympathomimetic, anticholinergic, and marijuana toxic effects (Table 2). The most common sympathetic nervous system cardiovascular effects are tachycardia (46%) and hypertension (21%). The anticholinergic effects closely overlap with signs and symptoms of a sympathomimetic toxidrome. Distinguishing symptoms specific to anticholinergic toxicity include dry skin, “cotton mouth,” absent bowel sounds, blurred vision, and urinary retention. Patients may also present with marijuana intoxicated symptoms (eg, ataxia, delayed reaction time, and conjunctival injection). Laboratory studies are indicated in cases of severe intoxication with agitation or seizures; the potential metabolic derangements that can result may be life-threatening.

Synthetic Cathinones

Colloquially known as bath salts, these agents are synthetic psychostimulants structurally related to cathinone, a monamine alkaloid found in the khat plant. They are commonly abused for their euphoric, empathogenetic, and stimulating effects. As substituted phenethylamines, synthetic cathinones are structurally and pharmacologically similar to amphetamine and 3,4-methylenedioxymethamphetamine (MDMA). The most commonly abused synthetic cathinones are 4-methylmethcathinone (mephedrone), 3,4-methylenedioxyn-N-methylcathinone (methylone), and 4-methylenedioxypyr rolone. Synthetic cathinones produce major effects on the central nervous system and are linked to adverse neuropsychiatric complications (Table 1). These agents stimulate the release of dopamine and inhibit the reuptake of epinephrine, norepinephrine, and serotonin, inducing a broad range of sympathomimetic, serotonergic, and hallucinogenic adverse toxidrome effects (Table 2). The most frequent sympathetic nervous system cardiovascular effects are tachycardia (46%) and hypertension (21%). The hallucinogenic effects (ie, perceptual distortions, depersonalization, synesthesia) can be highly distressing, often prompting emergency psychiatric care. Ancillary lab studies should be ordered in cases of severe agitation because of the increased risk for acute kidney injury, rhabdomyolysis, lactic acidosis, stroke, and intracranial hemorrhage.

General Management Principles

The diagnosis of intoxication is based on a history of exposure and presence of characteristic signs and symptoms. Patients may unknowingly or inadvertently administer synthetic cannabinoids and cathinones, as these compounds are often adulterated with other illicit drugs, such as MDMA. Patients will typically present with signs and symptoms of adrenergic neurohumoral activation. The neurotoxic symptoms (eg, aggression, confusion, and psychosis) may overlap with a primary mental illness; psychiatrists should rely on the clinical history and physical exam findings for an accurate diagnosis. In the setting of acute intoxication, urine immunoassay testing has a low positive predictive value for synthetic cannabinoids and cathinones. The molecular geometry of synthetic cannabinoids and cathinones is ever-changing, making it increasingly difficult to identify these compounds via gas chromatography/mass spectrometry, which may not be readily available to assist in the diagnosis process. An atypical onset of psychosis and agitation alongside hypersympathetic activation and a mixed toxidrome is strongly suggestive of intoxication.

Psychiatrists should strongly consider the possibility of intoxication in any patient with no known psychiatric history, a negative urine drug screen, and no known contributing medical mimickers presenting with a mixed toxidrome. Patients will not necessarily fit neatly into a particular toxidrome; rather, they present with overlapping signs and symptoms from multiple toxidrome classes. Consequently, differentiating synthetic cannabinoid and synthetic cathinone toxicity can be challenging. Regardless, supportive care and symptom management is the mainstay of the treatment. Benzodiazepines are considered the first line of treatment to reduce the sympathomimetic neural stimulation (eg, hypertension, agitation, and seizures). Addressing Agitation

Agitation is the most common neuropsychiatric complication associated with synthetic cannabinoid and cathinone ingestion. In fact, according to one report, 40% of intoxicated patients evaluated in an ED will experience severe agitation. The spectrum of psychomotor agitation can be objectively measured and identified with a standardized rating scale such as the Behavioral Activity Rating Scale (BARS). For patients with mild-to-moderate agitation (BARS score = 5 or 6), the patient may initially be calmed with verbal de-escalation

Table 1. Common Adverse Neuropsychiatric Effects of Synthetic Cannabinoid and Cathinone Intoxication

<table>
<thead>
<tr>
<th>Psychiatric symptoms</th>
<th>Estimated prevalence of patients experiencing synthetic cannabinoid reactions</th>
<th>Estimated prevalence of patients experiencing synthetic cathinone reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agitation/irritability</td>
<td>25%</td>
<td>40%</td>
</tr>
<tr>
<td>Lethargy</td>
<td>14%</td>
<td>7%</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>12%</td>
<td>13%</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>11%</td>
<td>18%</td>
</tr>
<tr>
<td>Delusions</td>
<td>11%</td>
<td>18%</td>
</tr>
<tr>
<td>Seizures</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Headaches</td>
<td>3%</td>
<td>3%</td>
</tr>
</tbody>
</table>
Hyperpyrexia and metabolic acidosis are considered the initial drugs of choice for decreasing agitation because of their rapid onset of action, short half-life, and parenteral route of administration availability. Antipsychotics are commonly administered with benzodiazepines to manage the psychotomimetic effects. However, risks associated with antipsychotics in acute poisoning settings must be carefully considered since they may increase the risk of seizure induction, have anticholinergic effects, impair temperature regulation mechanisms, and prolong the QTc interval. Serotonergic sedatives such as fentanyl should be avoided because of the increased risk of serotonin toxicity associated with synthetic cannabinoids and cathinones.

**Excited Delirium**

A systematic review reported that 25% to 94% of patients diagnosed with excited delirium were recently exposed to synthetic cannabinoids and/or cathinones. The American College of Emergency Physicians has provided guidance on evaluating excited delirium, for which a minimum of 6 to 10 clinical criteria are required to make a diagnosis. If undertreated, the case-fatality rate is estimated to be 20%, partly due to catecholaminergic cardiorespiratory failure. The cornerstone of treatment is rapid sedation to reduce the sympathomimetic outflow and facilitate lifesaving treatments.

To date, no large-scale randomized controlled trials have evaluated pharmacological treatments for excited delirium. Nonetheless, the standard of care is to administer benzodiazepines and antipsychotics to decrease psychomotor agitation. In the emergency setting, intramuscular (IM) ketamine (4-5 mg/kg) is increasingly used for sedation of agitated patients with excited delirium. Initial studies in the prehospital setting (emergency medical services) reported that intubation rates following ketamine administration were as high as 60%. Emerging literature supports that IM ketamine administration in the hospital setting (ie, ED) is a safe and effective treatment for excited delirium while not significantly affecting the cardiopulmonary system.

Mankowitz et al reported that more patients required intubation after ketamine administration in the prehospital setting (30%) compared with the hospital setting (1.8%). Prospective studies conducted in the ED have demonstrated that there is no significant difference in incidence of complications between IM ketamine and IM haloperidol.

The adverse effects of single doses of IM ketamine for agitation are generally transient and self-limiting; they include emesis, hypersalivation, recovery agitation (also known as emergence reaction), hypertension, and tachycardia. Moreover, ketamine has other potential benefits, including a faster onset to sedation compared with benzodiazepines and antipsychotics. There are observational reports of ketamine exacerbating psychosis in susceptible patients. Larger studies, however, have concluded that acute- and short-term ketamine administration for agitation does not increase psychiatric inpatient admissions or ED psychiatric evaluations. Physical restraints should be used as a last resort, primarily as a bridge to pharmacologic treatment, as prolonged use of physical restraints is likely to worsen delirium and rhabdomyolysis, as well as lead to renal failure, electrolyte abnormalities, and arrhythmias.

**Psychosis and Psychotic Reactions**

Synthetic cannabinoids have been linked to psychotic reactions, such as paranoia, catatonia, and dissociation, as well as auditory and/or visual hallucinations. Longitudinal studies have reported that consumption of potent cannabinoids quintuples the risk of a psychotic episode. The psychotomimetic effects are usually transient and resolve within 5 to 8 days; however, up to one-third of patients will transition to schizophrenia. Although there is no established antidote, preliminary reports suggest that cannabinol, an allosteric modulator at the CB1 receptor, may reverse the neurotoxic effects.

Similarly, synthetic cathinones have propylphencycotic effects, potentially triggering a psychotic state in vulnerable patients. An observational study reported that synthetic stimulants were implicated in approximately 25% of ED visits involving drug-related psychosis. Specifically, methylphened was the most common synthetic cathinone involved, accounting for approximately 20% of stimulant-related psychotic cases. Synthetic cathinone-induced psychosis is typically brief and resolves within days to weeks; however, 25% of patients will transition to a schizophrenia spectrum disorder.

The psychotomimetic symptoms can be controlled with first- and second-generation antipsychotic medications with careful consideration of adverse effect profiles. Among the first-generation antipsychotics, the butyrophenone neuroleptics IM haloperidol and IM droperidol are reasonable pharmacotherapeutic options. In comparison with IM haloperidol, IM droperidol has a faster onset of action; it rapidly prevents and treats emergent psychotic agitation within 5 to 10 minutes of IM administration. Some expert panels have recommended using butyrophenone neuroleptics in cases of substance-induced psychosis due to its proconvulsant properties, cardiovascular effects, and extrapyramidal symptoms.

Among the second-generation antipsychotics, ppolanzapine has a track record of treating NPS-induced psychosis, and produg websites have touted olanzapine as the ideal medication to terminate “bad trips.” In spite of its efficacy, olanzapine has anticholinergic and central thermoregulatory effects that impair core temperature regulation. In theory, po or IM aripiprazole and ziprasidone are probably the safest antipsychotics to administer because of their relatively favorable safety profile and negligible anticholinergic and seizuregenic effects.

Despite the infamous concerns about QTc prolongation, epidemiological studies do not support a correlation between ziprasidone and torsades de points. In many instances, detoxification with benzodiazepines and rest will often quell the substance-induced symptoms without the added need for antipsychotics. Given the risks associated with neuroleptics, especially in patients who are anti-psychotic naïve, it may be best to consider a benzodiazepine as the first-line agent to reduce the psychotic agitation. Antipsychotics can be initiated if the psychosis continues to persist after the detoxification period, or if the patient has an underlying primary psychotic illness.

**Conclusions**

Synthetic cannabinoid and cathinone harms are increasing. Synthetic cannabinoids and cathinones have propylphencycotic and agitative effects, and the toxic reactions can mimic a primary mental illness. Because no definitive diagnostic test differentiates primary vs secondary drug-induced mental illness, psychiatrists must rely on the history and physical examination.

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Addressing Apathy in Dementia

T he English word apathy originates from the Greek word ἀπαθεία, which means "without pathos or feeling." But scholars have shared various definitions. For example, Robert S. Martin, MD, defined apathy as a syndrome of primary motivational loss that is not attributable to emotional distress, intellectual impairment, or diminished level of consciousness. According to Drs Richard Levy and Bruno Dubois apathy is the quantitative reduction of self-generated voluntary and purposeful behaviors, which are observable and can be quantified. In addition, the underlying mechanism(s) responsible for apathy may be seen as dysfunctions occurring at the level of elaboration, execution, and control of goal-directed behaviors. According to an international consensus criterion, apathy is defined as a disorder of motivation in which the symptoms are present for at least 4 weeks. In addition, 2 of the following 3 should be present: reduced goal-directed behavior, reduced goal-directed cognitive activity, and reduced emotions. Furthermore, these symptoms cause clinically significant impairments in personal, social, occupational, or other important areas of functioning, with such symptoms not exclusively explained by or due to other causes (ie, reduced level of consciousness). 2 According to Drs Nordström K, Zan LS, Wilson MP, et al. Medical evaluation and treatment of agitation in agitated case series. BMC Psychiatry 2016;16:298. 2

In a systematic review, several studies showed that individuals with dementia without apathy had a significantly lower level of consciousness. 2 According to Drs Nordström K, Zan LS, Wilson MP, et al. Medical evaluation and treatment of agitation in agitated case series. BMC Psychiatry 2016;16:298. 2

Apathy was also seen as one of the most frequently reported behavioral symptom during the agitated behavior in patients with dementia. 1 Apathy is also associated with increased risk for death among individuals with dementia.13

Epidemiology

Apathy is seen in approximately 1.4% to 15.8% of individuals who have no cognitive deficits. It is also seen among individuals with major depressive disorder, schizophrenia, strokes, multiple sclerosis, and traumatic brain injury. Apathy is more prevalent among individuals with neurodegenerative disorders than those in free of such disorders.9 Apathy has been noted throughout the spectrum of neurocognitive disorders (Figure). The prevalence rates for apathy among individuals with mild cognitive impairment ranges from 3.1% to 50.5%. Apathy is also the most frequently reported behavioral symptom among individuals with dementia. The results of one study showed that individuals with frontotemporal dementia (FTD) and vascular dementia (VaD) report more severe apathy than individuals with Alzheimer disease (AD).12

Apathy usually appears early in dementia and tends to persist throughout; it is associated with longer illness duration and it worsens with the progression of dementia.2 Risk factors for developing apathy include older age and greater severity of cognitive impairment. Aloyd et al found that apathy was correlated with the degree of cognitive impairment among individuals with AD and VaD, but not with FTLD; but apathy did not correlate with age or gender in individuals with AD, FTLD, and VaD. Additionally, the degree of apathy correlated with the level of functional impairment and dementia severity across all 3 types of dementia.14

Individuals with dementia who present with apathy often have more rapid cognitive decline and are more impaired in their activities of daily living. In addition, apathy increases the risk for earlier institutionalization among individuals with dementia.15 Distress is also significantly higher among caregivers of individuals with dementia who have apathy, when compared with individuals with dementia without it.16 Apathy is also associated with increased risk for death among individuals with dementia.13

Neurobiology

Emerging evidence indicates that apathy in individuals with dementia occurs due to a complex interaction among neuroanatomy, neurophysiology, neurochemistry, and genetics. Among individuals with AD, apathy is associated with an increased neurofibrillary tangle burden in the parahippocampal, frontal, and parietal regions, in addition to the anterior cingulate gyrus. Emerging evidence indicates that the severity of apathy is also associated with amyloid plaque burden, especially in bilateral frontal cortices and the right anterior cingulate gyrus along with other cortical areas of the brain.15,16

One study that evaluated the cerebrospinal fluid (CSF) biomarkers among individuals with AD showed that apathy was significantly correlated with tau and p-tau, but not with amyloid β-1-42. Another study examined regions of cortical thinning and CSF biomarkers (amyloid-β-1-42, total tau, and phosphorylated tau) among 3 groups—clinically normal elderly individuals, individuals with mild cognitive impairment, and individuals with mild AD dementia with apathy—and found that reduced baseline inferior temporal cortical thick-
ness was predictive of increasing apathy over time. The investigators of this study did not find any association between CSF biomarkers and the severity of apathy in cross-sectional or longitudinal analyses.

Another study found that individuals with AD and apathy had a loss of white matter integrity in the genu of the corpus callosum when compared with individuals with AD without apathy. In addition, the loss of white matter integrity in the genu, body, and splenium of the corpus callosum was negatively correlated with the severity of apathy among individuals with AD. Neuropsychological studies indicate that the dysfunction of the anterior cingulate cortex is the strongest anatomical correlate of apathy in AD, whereas lesions of the basal ganglia are the most common correlates of apathy in cerebrovascular disorders.

Neuroimaging studies indicate that the apathy among individuals with behavioral variant of FTD is associated with prominent atrophy in: the dorsal anterior cingulate cortex, dorsolateral prefrontal cortex, right caudate (including the ventral striatum), right temporoparietal junction, right posterior inferior and middle temporal gyri, and left frontal operculum-anterior insula region.

A recent meta-analysis that analyzed data from 41 studies indicated that apathy is associated with hypometabolism and a decrease in gray matter volume in the left inferior frontal gyrus. The investigators also found altered brain perfusion and decreased gray matter volume in the anterior cingulate cortex among individuals with AD, and decreased gray matter volume in the inferior frontal gyrus and parietal cortex among individuals with FTD. These findings indicate that apathy occurs due to a cortical dysfunction of areas involved with executive cognitive processing (action planning) and emotional regulation (autoactivation and reward processing).

Individuals with AD and apathy have been found to have reduced dopaminergic activity in the putamen, reduced acetylcholine in the lateral frontal cortex, and lower levels of plasma gamma-aminobutyric acid. In evaluating the association between apolipoprotein E ε4 allele and apathy in probable AD, investigators found that the presence of this allele was indeed significantly associated with apathy in these individuals.

Assessment
Among individuals with dementia, the assessment of apathy is often complicated. It is particularly difficult to distinguish between reduced motivation to do things due to apathy and the loss of ability or motivation secondary to cognitive dysfunction. Additionally, there may be overlap between symptoms of apathy and depression (Table 1). Often, as well, psychotropic medications (ie, antidepressants) are used to treat neuropsychiatric symptoms (NPS) of dementia, and the adverse effects of these medications include fatigue, lethargy, listlessness, and decreased initiative to respond to external stimuli. These AEs can mimic symptoms of apathy among individuals with dementia.

The scales that have been developed for the assessment of apathy include the Apathy Evaluation Scale (AES), the Structured Clinical Interview for Apathy, the Apathy Scale, the Apathy Inventory, the Dementia Apathy Interview and Rating (DAIR), and the Lille Apathy Rating Scale (LARS). Among these scales, only the DAIR was designed for use among individuals with dementia. The Apathy Scale for Dementia Patients in Nursing Homes was designed to measure apathy among individuals with dementia who live in institutional settings. The Neuropsychiatric Inventory (NPI) is considered the gold standard for the assessment of NPS among individuals with dementia. However, the use of a single domain from the NPS prevents a comprehensive assessment of all dimensions of apathy among individuals with dementia. A recent systematic review found that the DAIR, the AES–clinical version (AES–C) in AD, and the LARS in Parkinson disease (PD) had psychometrically favorable qualities and the highest quality among the scales used to assess apathy among individuals with neurodegenerative disorders.

Treatments
Available evidence indicates that both nonpharmacological and pharmacological treatment modalities can benefit individuals with dementia who present with apathy (Table 2).

A systematic review by Brodaty et al found that therapeutic activities—including stimulation, creative activities, cooking, Montessori methods, music, exercise, multisensory stimulation, and pet therapy—as well as placement in special care units may improve apathy among individuals with dementia. Another recent systematic review by Cai et al, evaluating the effectiveness of nonpharmacological interventions among individuals with dementia and apathy, also found that multisensory stimulation, music therapy, cognitive stimulation, and pet therapy are useful in improving symptoms of apathy. Cai et al found limited evidence as well for the efficacy of art, exercise, reminiscence, and occupational therapies; dementia special care units; comprehensive interventions; nursing staff education; and behavioral management techniques (ie, therapeutic conversations, progressive muscle relaxation). They found that the effects of psychomotor therapy and validation therapy were still unclear; evidence also indicates that receptive music therapy is better than interactive music therapy. Pet therapy that includes the introduction of domestic pets and companion robots tends to reduce loneliness and improve well-being. Tailoring the overall lifestyle of individuals with dementia to increase recreational activities, physical exercise, cognitive stimulation, and social activities also reduces apathy.

Various pharmacological agents have been trialed for the treatment of apathy, including acetylcholinesterase inhibitors (ChEIs), memantine, stimulants, calcium antagonists, and antipsychotics. In their systematic review and meta-analysis, Sepehry et al found a total of 15 randomized controlled trials that assessed the efficacy of pharmacotherapy. For cognitive enhancers (donepezil and galantamine), there was no significant effect of treatment on apathy (Hedges’ g = −0.055; P = .687). The average donepezil dosage was 10 mg/day, while galantamine dosage ranged between 16 mg/day and 32 mg/day. All but 1 study used the NPI-apathy subscale as an outcome measure, and these trials included individuals with mild-to-severe AD. For memantine, the investigators found a small and nonsignificant benefit for apathy (Hedges g =.092; P = .423). The average dose of memantine was 20 mg/day, and the trials included individuals with moderate-to-severe AD and used the NPI-apathy subscale. The effect of psycho-stimulants on apathy was small and nonsignificant when compared with placebo (Hedges’ g =−.063; P = .903). All stimulant trials included individuals with mild-to-moderate AD, used multiple scales including the NPI-apathy and Frontal Systems Behavior Scale (FrSBe) apathy subscale, and included mixed drugs with non-comparable dosages. The investigators did not find enough individual

### Table 1. Distinguishing Depresison From Apathy

<table>
<thead>
<tr>
<th>Symptoms common to depression and apathy</th>
<th>Symptoms specific to depression</th>
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<tbody>
<tr>
<td>Reduced interest in activities</td>
<td>Dysphoria</td>
</tr>
<tr>
<td>Psychomotor retardation</td>
<td>Self-criticism</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Feelings of guilt</td>
</tr>
<tr>
<td>Hypersomnia</td>
<td>Pessimism</td>
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<tr>
<td>Lack of insight</td>
<td>Hopelessness</td>
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<tr>
<td></td>
<td>Suicidal ideation</td>
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</table>

### Figure. Apathy Among Individuals With Neurocognitive Disorders

<table>
<thead>
<tr>
<th>Neurocognitive Disorder</th>
<th>Range of Apathy Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer Disease</td>
<td>30% - 70%</td>
</tr>
<tr>
<td>Vascular Dementia</td>
<td>15% - 20%</td>
</tr>
<tr>
<td>Frontotemporal Dementia</td>
<td>17% - 70%</td>
</tr>
<tr>
<td>Parkinson Disease</td>
<td>16% - 67%</td>
</tr>
<tr>
<td>Dementia with Lewy Bodies and Progressive Supranuclear Palsy</td>
<td>17% - 89%</td>
</tr>
<tr>
<td>Corticobasal Degeneration</td>
<td>40%</td>
</tr>
<tr>
<td>Huntington Disease</td>
<td>34% - 76%</td>
</tr>
</tbody>
</table>
studies to do a meta-analysis for antipsychotics and drug classes with antidepressant properties, but the data from the individual atypical antipsychotic studies did not support their use for apathy in AD. The investigators indicated that the analysis for cognitive enhancers and memantine were appropriately powered, whereas the psychostimulant studies were underpowered due to limited patient enrollment in each arm of the trials.

In another quantitative meta-analysis, Rushakova et al included data from 21 studies. The investigators found that methylphenidate may improve apathy when compared with placebo; this held true when apathy was assessed using the AES (mean difference [MD] = – 4.99) but not when using the NPI-apathy subscale (MD = – 0.8).

The investigators further found that methylphenidate may also improve cognition (MD = – 0.08) and instrumental activities of daily living (MD = 2.30), when compared with placebo. There was no difference between methylphenidate and placebo in the risk of developing an adverse event (risk ratio = 1.28). The investigators indicated that the combination of cilupram and memantine reduced apathy among individuals with AD when compared with placebo.28

Concluding Thoughts

Apathy can be described as the quantitative reduction of self-generated voluntary and purposeful behaviors that are observable and quantifiable. Apathy commonly presents in individuals with many different illnesses, including major depressive disorder, schizophrenia, strokes, multiple sclerosis, and traumatic brain injury. However, apathy is more prevalent among individuals with neurodegenerative disorders, including dementia. Among individuals with dementia, apathy is considered to be the most frequently reported behavioral symptom. Apathy worsens morbidity and mortality in AD and is associated with greater caregiver distress.

The exact neurobiological mechanisms associated with apathy in dementia are unclear, but emerging evidence indicates a complex interaction among neuroanatomy, neuropsychology, neurochemistry, and genetics. The assessment of apathy is often complicated, and it is difficult to distinguish between reduced initiative to do things due to the loss of cognitive ability vs the loss of motivation due to apathy. In addition, there may be an overlap between symptoms of apathy and depression. Among many scales that have been developed to assess apathy, the DAIR, the AES-C in AD, and the LARS in PD have the highest quality. Emerging evidence indicates efficacy for both nonpharmacological and pharmacological treatments for improving apathy. Multisensory stimulation, music therapy, cognitive stimulation, and pet therapy are beneficial nonpharmacological treatments; and among pharmacotherapy options, ChEIs may be the best available treatment choice, followed by gingko biloba, memantine, and stimulants like methylphenidate either alone or in combination with ChEIs. Future directions in the evaluation of apathy in dementia should include the study of animal models as well as genetic studies that improve the knowledge of the neurobiological mechanisms underlying this condition. In addition, well-designed clinical trials of nonpharmacological and pharmacological interventions that exclusively target apathy in dementia are needed. These trials should assess not only the symptomatic improvement of apathy but also evaluate its effect on the individual’s functioning and on caregiver burden. These studies should use advances in both neuroimaging techniques and biomarkers to provide surrogate metrics for treatment response.

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REFERENCES


Table 2. Selected Pharmacotherapy and Nonpharmacological Treatments
Faith Communities and the Well-being of LGBTQ Youth

Michael A. Norko, MD, MAR

In March 2021, the Board of Trustees of the American Psychiatric Association voted to commend the Group for the Advancement of Psychiatry (GAP) for its contribution to the well-being of LGBT youth, applauding the Psychiatry and Religion and LGBTQ+ committees of GAP for their booklet, Faith Communities and the Well-being of LGBT Youth. Published online, the booklet addresses ways in which faith leaders and faith communities can support LGBT youth in their communities to mitigate mental health challenges.

Nearly 5 years ago, a friend of mine was discussing the problem of suicides in LGBT youth with his local bishop. The bishop asked whether there were any documents from mental health experts that might address this concern. My friend related the query to me because of my previous LGBT advocacy in a religious context. Since I was not aware of such a resource, I contacted Mary Barber, MD, of the GAP LGBT Committee, and she pointed me to the work of Caitlin Ryan, PhD, and the Family Acceptance Project (FAP). That began a collaboration among the 2 GAP committees and Ryan, resulting in a booklet to meet this need.

The booklet acknowledges the common interests shared by medicine and religion in the welfare of young individuals. Then, it describes multiple mental health challenges faced by LGBT youth, including suicide, depression, anxiety, substance use, bullying, and homelessness. Included are data showing that, in comparison with peers who are not in a sexual minority, LGBT youth are about twice as likely to be bullied or use illicit drugs, more than twice as likely to feel persistently sad or hopeless, more than 3 times as likely to inject illegal drugs and consider suicide or make a suicide plan, and more than 4 times as likely to attempt suicide. The booklet discusses the factors contributing to stress, including those relevant to a specific religious context—such as being unable to marry within one’s faith or to be open in one’s faith community—and being rejected by family and community more broadly. Faith traditions vary in their teaching about sexual orientation and same-sex marriage, but no faith tradition wishes to intentionally harm its young members or to discourage them from engaging behaviors within one’s faith or to be open in one’s faith community and is provided for further inquiry and discussion.

The GAP booklet is written to apply more broadly to members of any faith community and is offered as a joint concern of faith communities and health care providers and organizations, but some faith communities are already adopting the materials and tailoring them. FAP produced a booklet about the welfare of LGBT children directed specifically to members of the Mormon Church. The Evangelical Lutheran Church of Finland has agreed to consider publishing a version of the booklet translated into Finnish, with additional local resources and research. Psychiatrists can contribute to their own communities by becoming familiar with the booklet and its underlying evidence base.

Dr Norko is chair of the Psychiatry and Religion Committee of GAP and professor of psychiatry at Yale University School of Medicine, where he specializes in forensic psychiatry. In 2010, he earned a master’s degree in religion from Yale Divinity School.

REFERENCES


Athough cognitive difficulties may not be the primary symptom addressed in patients with schizophrenia, these impairments are a central feature that can contribute to social and functional disability. Cognitive dysfunction in schizophrenia affects not only attention, verbal memory, reasoning, and processing speed, but also social cognition and interactions. Thus, the topic has received increased attention. (For more information, see the Psychiatric Times® Cognition Special Report in the December 2020 issue—Ed.)

A growing body of research results indicates viruses may play a role in both schizophrenia and cognitive difficulties. One in particular, Epstein-Barr virus (EBV), has received notable attention in the possible pathophysiology of schizophrenia as well as of associated cognitive dysfunction, although findings have been inconsistent. For instance, in a previous study of 229 patients with schizophrenia, the data did not indicate an association between EBV seropositivity and cognitive performance. Importantly, previous studies have generally measured exposure by reactivity to a single EBV protein, rather than to a panel of proteins or EBV virions. EBV, also known as human herpesvirus 4, is a lympohotropic virus that can produce acute and latent infections.

The Study
Using the MATRICS Consensus Cognitive Battery (MCCB), Dickerson and colleagues’ tested their hypothesis that antibodies to various EBV proteins may be associated with different levels and domains of cognitive functioning in patients with schizophrenia. Patients with schizophrenia or schizoaffective disorder were enrolled at the Stanley Research Program at Sheppard Pratt in Baltimore, Maryland, in 1 of 3 trials of adjunctive medications for adults with schizophrenia that were conducted between 2014 and 2019. Across the 3 trials, inclusion criteria were: receiving outpatient (vs inpatient) treatment; aged > 18 years; diagnosis of schizophrenia/schizoaffective disorder confirmed by structured clinical interview; and current stable antipsychotic treatment. Patients were excluded from the study if they had clinically significant or unstable medical disorders; were pregnant or breastfeeding; had current or recent substance use disorder; or were found to have an intellectual disability or IQ below 70 (Table 1). In addition to the MCCB, the psychopathology of each patient was assessed using the Positive and Negative Syndrome Scale (PANSS). The total sample size was 84 (Table 2).

Blood was assayed for immunoglobulin G antibodies to EBV antigens derived from intact virions using enzyme immunoassay. Assay values for patients were compared with a standard score based on the reactivity of controls without psychiatric disorders. Reactivity to herpes simplex virus type 1 (HSV-1) was also measured by immunoassay. In all studies, blood samples and cognitive testing were completed before the administration of any study medications, clinicians can potentially improve cognitive outcomes by optimizing antipsychotic dosing.
Table 3. Cognitive Domains in Schizophrenia Assessed by the MCCB

<table>
<thead>
<tr>
<th>Domains</th>
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<tr>
<td>Processing speed</td>
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<tr>
<td>Attention/vigilance</td>
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<td>Working memory</td>
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<tr>
<td>Verbal learning</td>
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<tr>
<td>Visual learning</td>
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<tr>
<td>Reasoning and problem solving</td>
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<tr>
<td>Social cognition</td>
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<tr>
<td>Composite/global cognition</td>
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</table>

Based on symptoms and adverse effects, treating underlying depression, facilitating treatment of medical comorbidities (eg, hypertension, diabetes), and utilizing other therapies (eg, cognitive remediation) as available and appropriate.

Dr Miller is a professor in the Department of Psychiatry and Health Behavior of Augusta University in Augusta, Georgia. He is on the Editorial Board and serves as the schizophrenia section chief for Psychiatric Times. The author reports that he receives research support from Augusta University, the National Institute of Mental Health, the Brain and Behavior Research Foundation, and the Stanley Medical Research Institute.

REFERENCES

BIPOLAR UPDATE
Shining a Spotlight on Bright Light for Acute Bipolar Depression

David N. Osser, MD

Have you run out of ideas for your outpatient with resistant bipolar depression? You might consider the results of an interesting study about the use of bright fluorescent light.1

There have been a fair number of previous studies on light therapy for bipolar disorder. Some studies with this modality of treatment, when compared with likely inactive controls, have not shown efficacy for patients whose disease does not have a seasonal component. Other reports suggested a high rate of switching to mania in patients with bipolar disorder when they received early morning light (the usual timing for light treatment targeting nonbipolar depression). Fortunately, 2 studies showed good results for chronotherapy; in these studies, patients were kept up all night and then administered morning light.2 However, midday light might be safer and/or more efficacious based on some theoretical considerations, and more acceptable compared with requiring sleep deprivation.

In a small study of midday light, 46 patients with moderate bipolar depression were randomized to 1 hour of bright white light at noon (7000 lux, which is less than the 10,000 lux usually administered for unipolar depression) or 50 lux dim red placebo light for 6 weeks.1 Patients exhibiting mixed features, as well as those with a history of rapid cycling in the past year, were excluded from the study.

Patients with active suicidal ideation, those with any substance use disorder in the past 6 months, and those on melatonin, stimulants, or nonsteroidal anti-inflammatory drugs were also excluded. Thus, at best, the study results apply to a very limited number of patients in comparison with usual practice patients.

The light dose was titrated slowly as a precaution against inducing mania. Participants started with a 15-minute treatment, which increased by 15 minutes weekly until reaching 1 hour at week 4. Most other light treatment protocols start with the full dose, so this was another novel aspect of the approach (in addition to the timing of the light).

The results demonstrated that remission (defined as a score of 8 or less on the primary depression rating scale) was seen by week 6 in 68% of the bright light group vs 22% of the control group. There were no mood polarity switches. Quite notably, there was no difference between the active and placebo groups in the first 3 weeks. Remission in other light therapy studies tends to cluster at week 3, so the time frame for improvement was similar to other protocols despite the ramping up of dose over the first 4 weeks. However, based on the improvement difference seen between active and placebo groups in weeks 4 to 6, it seemed likely that more treatment time could have resulted in further remissions for the treatment group. The findings were characterized as robust, which is a term rarely encountered for studies of bipolar depression (except, perhaps, for electroconvulsive therapy).2

Effort was made to prevent bias among patients regarding their expectations of the bright light compared with the dim red light. Recorded baseline levels of expectations were equal in the 2 groups and did not change when repeated at study completion. Nevertheless, one cannot be extremely confident that the blind was successful when the treatments looked so different.

Nothing is known about what strategies to employ with midmorning light for maintenance of the therapeutic effects.

The caveat should be offered that new treatments often do well in early studies, but then those results are harder to replicate in subsequent and larger studies. Examples of such include valproate and prazosin.3,4

Dr Osser is associate professor of psychiatry, Harvard Medical School, and co-lead psychiatrist at the US Department of Veterans Affairs, National Telemental Health Center, Bipolar Disorders Telehealth Program, Brockton, Massachusetts. He also serves as a member of the Editorial Board of Psychiatric Times. Dr Osser has no financial disclosures regarding this article.

REFERENCES
Prognostic Considerations in Anti-NMDA Receptor Encephalopathy With Psychiatric Manifestations

Michael C. Li, MD; James A. Bourgeois, OD, MD

In recent years, a growing body of literature has described autoimmune encephalitis as an important, if infrequently seen, cause of subacute onset of psychotic illness in patients. One of the important syndromes in this group is anti-NMDA (N-methyl-D-aspartate) receptor encephalitis (ANMDARE). As patients experiencing ANMDARE may experience exclusively psychiatric symptoms (eg, psychosis, depressive symptoms), they will likely initially present to psychiatrists. The psychiatrist therefore must consider various components of the presentation in clinical evaluation and management.

Psychotic and depressive illnesses are common in the population, compared with ANMDARE. Consequently, psychiatrists must decide which patients warrant consideration of ANMDARE and the associated diagnostic studies, which are quite detailed and not part of a typical workup for psychotic and depressive disorders. Three broad areas can guide the physician: atypicality of presentation, comorbid neurologic symptoms and signs, and other systemic medical comorbidity commonly reported in ANMDARE. Ultimately, clinical intervention, treatment approaches, and surveillance for recurrence and prognosis will need to be considered.

Presentation and Diagnosis

Atypicality of presentation is an inherently imprecise construct, in that it refers to how a given case presents differently from other more common presentations of the same illness. Herein lies the conceptual challenge. Understanding the construct of atypicality requires the clinician to apply an initial classification template to the overall gestalt of a case. For psychotic illness, the physician starts with an observation of the primacy of disordered reality testing (eg, delusions, hallucinations) and thought process (eg, looseness of associations, thought blocking, disorganization) in patient presentation. The primacy of the psychotic symptoms must outweigh other psychiatric findings (eg, depressive, anxiety, cognitive symptoms) so as to define the case as psychotic disorder.

Once psychiatrists apply the general template, they may notice that the details of the case do not quite fit. Hence, atypicality. Atypicality may in-
clude epidemiologic features (eg, psychotic symptoms occurring at a later-than-typical age of onset; psychotic illness in a patient with no similar family history), course of presentation (eg, a patient with abrupt onset of psychosis that develops rapidly to impair function without a prodromal state), and social context (eg, onset of psychotic illness without notable social stressors temporally associated with illness onset).

Comorbid neurologic symptoms and signs should be routinely considered in any psychiatric evaluation; after all, psychiatric illnesses are, by definition, brain diseases. Specific consideration of motor signs, sensory symptoms, seizures, and disorders of arousal and attention should be considered. The more coincident neurologic comorbidities that are present, the greater the likelihood of ANMDARE and other neuropsychiatric illnesses will be as a central explanatory hypothesis.

Finally, it is important to consider comorbid systemic (ie, non-central nervous system) illness. Psychotic illness occurring in the presence of rheumatologic illness with the use of immunomodulators, endocrinologic illness (eg, hypothyroidism), and/or with concurrent neoplasms raises the odds that the psychotic presentation may be directly attributable to systemic factors being etiologically associated with an illness with an apparent primary psychotic psychiatric presentation.

Prognosis and Treatment
To make an ANMDARE diagnosis, it is important to consult with a neurologist to obtain a lumbar puncture for cerebrospinal fluid (CSF) studies, magnetic resonance imaging (MRI) (unless the psychiatrist has already obtained it), and electroencephalography (EEG). Once the diagnosis is rendered, clinical intervention needs to be coordinated with other physicians. Clinicians should use antipsychotic and antidepressant medication to address manifest symptoms, but there is a likelihood that systemic immunomodulation therapies (eg, corticosteroids, intravenous immunoglobulin [IVIG], plasma exchange) may ameliorate the psychotic symptoms, such that long-term maintenance with antipsychotic or antidepressant medication may not be indicated. Similarly, resection of an ovarian teratoma may lead to improvement in symptoms.1,3

The prognosis for recurrence of atypical psychiatric illness due to ANMDARE is likely different from recurrence in more common psychiatric illness. In known ANMDARE, vigilance for recurrence should be permanent and lifelong. Recurrence of any clinically significant psychiatric illness should prompt reevaluation of neurologic and systemic medical status via a coordinated effort by the various physician specialties, while empirically treating the presenting symptoms. This is analogous to a patient with a known history of thyroid disease, wherein a recurrence of psychiatric symptoms mandates a prompt reevaluation of thyroid status and consideration of a change in endocrinologic treatment in addition to empiric use of psychotropic medications.1,3

Lessons From the Literature
The growing literature on recurrence and prognosis in ANMDARE can guide the psychiatrist in management of these patients over time (Table 1).

Pollak and colleagues presented an integrated approach to the identification of possible, probable, and definite autoimmune psychoses and outlined the options for their appropriate diagnosis and management.1 Psychiatric symptoms consistent with possible autoimmune encephalitis include abrupt onset of psychosis (with rapid progression within 3 months); movement disorder (eg, catatonia, dyskinesia); adverse response to antipsychotics, raising suspicion of neuroleptic malignant syndrome; disproportionate cognitive dysfunction; as well as decreased level of consciousness.

A diagnosis of probable or definite autoimmune encephalitis would further require confirmatory CSF, MRI, and/or EEG studies. Comorbid, nonpsychiatric red flags (eg, infectious prodrome, severe headache, focal neurologic signs, dysautonomia, tumor, hyponatremia, and other autoimmune disorders) should arouse suspicion of autoimmune encephalitis.3 The preferred treatment of psychosis in the acute phase is with second-generation antipsychotics, starting at low doses and titrating slowly. Benzodiazepines are indicated in the management of catatonia and in unclear cases of psychosis or aggression. Electroconvulsive therapy (ECT) has shown to be helpful in some cases for rapid symptom control.

If neuronal autoantibody seropositivity is the only abnormality, treatment with immunotherapy

<table>
<thead>
<tr>
<th>Study and design</th>
<th>Participants and follow-up</th>
<th>Intervention</th>
<th>Outcome measures</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huang et al2; literature review</td>
<td>N/A</td>
<td>N/A</td>
<td>Prognostic factors and treatment</td>
<td>1 Poor prognostic factors include older age and ICU admission. Antibody titers may persist months to years after treatment. 2 First-line immunotherapy includes IVIG, plasma exchange, and high-dose corticosteroids; second-line therapy includes rituximab and cyclophosphamide. 3 Third-line therapy includes tocilizumab, methotrexate, bortezomb, azathioprine, and mycophenolate.</td>
</tr>
<tr>
<td>Wang et al3; literature review</td>
<td>N/A</td>
<td>N/A</td>
<td>Prognostic factors and treatment</td>
<td>1 Abnormal EEG readings (eg, EDBs) do not correlate with final clinical outcome. 2 FDG-PET has a high sensitivity for identifying the most severe forms of ANMDARE. 3 The improvement of symptoms after treatment has not been found to be associated with a decline in antibody titers. 4 First-line immunotherapy includes IVIG, plasma exchange, high-dose corticosteroids; second-line therapy involves rituximab, cyclophosphamide, azathioprine, and mycophenolate mofetil; third-line therapy involves methotrexate, bortezomb, and tocilizumab. 5 Early initiation of immunotherapy and tumor removal is recommended. ICU admission is a poor prognostic factor.</td>
</tr>
<tr>
<td>Bradley et al4; literature review</td>
<td>2823 patients with autoimmune encephalitis (multiple mechanisms, including ANMDARE in 1566 patients)</td>
<td>N/A</td>
<td>Prognostic factors</td>
<td>ANMDARE prognosis was worse with: 1 Delay in or no intervention with immunotherapy; 2 Altered level of consciousness; and 3 ICU admission.</td>
</tr>
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</table>
may be dangerous and is therefore not recommended. Treatment should be considered on a case-by-case basis following evaluation by a team of neurologists and psychiatrists. Circulating antibodies should be removed via tumor removal, plasma exchange, immunosuppression, or IVIGs, followed by immunosuppression (with either steroids or steroid-sparing immunomodulating agents such as azathioprine, methotrexate, or mycophenolate mofetil).

Utilizing a study of 382 patients with ANMDARE, Bala and colleagues constructed a grading score for predicting a patient’s neurologic function 1 year after diagnosis of ANMDARE. The study results indicated that intensive care unit (ICU) admission, treatment delay > 4 weeks, lack of clinical improvement within 4 weeks, abnormal brain MRI suggestive of encephalitis, and CSF white blood cell count > 2 cells/µL were independent predictors for outcome. Poor functional status was defined as a modified Rankin Scale (mRS) score ≥3, and good functional status was defined as mRS score ≤2. Each of the 5 variables was equally weighted at 1 point each to construct a 5-point anti-NMDAR Encephalitis One-Year Functional Status (NEOS) score. The NEOS score was strongly associated with the probability of poor functional status at 1 year (Table 2). These findings suggest that the NEOS score accurately predicts 1-year functional status and should be used to estimate the velocity of clinical improvement, not the ultimate clinical outcome.

A retrospective case-control study looked at the sensitivity and specificity of serum and CSF antibody testing in patients with ANMDARE as well as the correlation among titers, relapses, and event outcome. The study included 250 patients with ANMDARE and 100 control participants. All 250 patients had NMDAR antibodies in CSF, but only 86% of patients had antibodies in the serum. CSF and serum titers were higher in patients with poor outcome as well as in those with teratoma. Over time, there was a decrease of antibody titers regardless of outcome. Relapse correlated better with titer change in CSF than that in serum. The findings suggest that NMDAR antibody testing is more sensitive using CSF than using serum. Antibody titers in CSF and serum are higher in patients with poor outcome or teratoma.

Huang et al conducted a literature review examining the prognostic factors and treatment of ANMDARE. They found that the proportion of patients with deficits during long-term follow-up ranged from 27% to 85% and the recurrence rate ranged from 12% to 29%, with a median interval of 2 years. Most patients responded well to first-line treatment and tumor removal. When first-line immunotherapy fails, second-line immunotherapy can improve outcome. Immunomodulators and tumor removal are effective for pregnant patients. Benzodiazepines are preferred for patients with catatonia, and ECT may be used when pharmacological treatment fails.

Further, Huang and colleagues found that older age and ICU admission were poor prognostic factors. They also found that antibody titers may not be early or sensitive biomarkers, as most patients will still have anti-NMDAR antibodies in the CSF and serum for months to years after treatment. Instead, early prognostic biomarkers included cell-free mitochondrial DNA, interleukin-17, YKL-40 (chitinase 3-1 like), neuron-specific enolase, and S100 calcium-binding protein B; the presence of any of these means a poor response to immunotherapy is more likely. The literature also indicated that those who did not receive adequate immunotherapy to treat the first episode were more likely to relapse. First-line immunotherapy treatments include IVIG, plasma exchange, and high-dose corticosteroids. Second-line treatments should include rituximab and cyclophosphamide. Third-line therapy includes tocilizumab, methotrexate, bortezomib, azathioprine, and mycophenolate mofetil, many of which have not been systematically verified in large cohorts.

A retrospective cohort study of 571 patients with ANMDARE found that 23 patients (4%) developed isolated psychiatric episodes: 5 at disease onset and 18 during relapses (Figure). Brain MRI was abnormal in 45% of these patients, and CSF showed pleocytosis in 77%. Furthermore, 83% had substantial recovery after immunotherapy and tumor resection when appropriate. After relapse, 94% of patients improved or returned to a similar or better relapse-free functional level. These findings suggest that isolated psychiatric episodes are rare, but they can occur as initial onset or relapse of ANMDARE. Patients with new-onset psychosis, history of encephalitis, subtle neurological symptoms, and/or abnormal ancillary tests should be screened for NMDAR antibodies.

In another retrospective cohort study that included 60 patients with ANMDARE, results showed that age ≥ 25 years, disturbance of consciousness at admission (defined as Glasgow Coma Scale < 5), and ≥50 slow waves (4-8 Hz theta waves or 0.5-4 Hz delta waves) on EEG were significantly associated with poor patient outcome. These 3 factors make up the 5-point age, consciousness, and slow waves (ACS) composite score, which are scored with 1, 1, and 2 points, respectively. An ACS/3 or ACS ≥3 meant a poor prognosis, defined as mRS score ≥3, whereas an ACS <3 meant a good prognosis, defined as mRS score ≤2. The ACS score was determined to have a sensitivity of 84% and specificity of 74%. The study found 36% of patients had good prognoses. These results suggest that the ACS score may be used to predict the early-stage prognosis of patients with ANMDARE.
Although ANMDARE usually presents initially as an abrupt onset of psychosis with comorbid neurologic symptoms and/or systemic symptoms, recurrent episodes may present in rare cases, as an isolated change in mood or behavior.

“Although ANMDARE usually presents initially as an abrupt onset of psychosis with comorbid neurologic symptoms and/or systemic symptoms, recurrent episodes may present in rare cases, as an isolated change in mood or behavior.”

positive for a while even after recovery. The relationship among CSF antibody titer, prognosis, and relapse still requires further research. Treatment includes early initiation of immunotherapy and tumor removal, both of which expedite recovery and decrease ANMDARE recurrence risk. Wang et al found that those who required ICU support had a poorer prognosis.

Wang and colleagues conducted a retrospective cohort study to better understand the effectiveness and adverse effects (AEs) of the treatment options.10 The study included 30 patients who tested CSF positive for ANMDARE, results showed that a majority of patients (83%) had early psychiatric symptoms, including agitation and psychosis within the first week of admission and 3 cases of catatonia within the second week. These patients were treated with antipsychotics (67%), with an average daily olanzapine equivalence dose of 11.5 mg, prior to immunomodulation therapy.

Although there was an 88% reduction in cases with aggression, antipsychotics alone provided little improvement in psychosis, affective symptoms, or catatonia.

Wang et al found no significant difference in the rate of occurrence of neurological and autonomic symptoms (ie, extrapyramidal symptoms [EPS] and neuroleptic malignant syndrome [NMS]) between those who received antipsychotics (20 patients) vs those who did not receive them (5 patients). Four patients experienced a possible recurrence of encephalitis: 1 who had seizures and 3 others with cognitive deterioration, mild movement disturbance, and recurrence of psychosis despite being continued on antipsychotic medications. All 4 cases resolved with immunomodulation therapy.

These findings suggest a need for psychiatric care for those with ANMDARE in both acute and chronic phases. Antipsychotic medications should be considered an adjunct to immunomodulation therapy. Suspected NMS and EPS cannot be differentiated easily from clinical progression of ANMDARE. Clinical reevaluation, careful withdrawal of potential causative agent, and immunomodulation therapy should be considered. Psychiatric management and psychotropic medication choice must be flexible, with dosing modifications depending on the most pressing psychiatric symptom, stage of illness, neurological symptoms, and risks of adverse effects.

In a prospective case-control study, Zhu and colleagues studied the CD138 levels as well as many other biomarkers in the serum and CSF of patients with ANMDARE.11 CD138 is a component of the endothelial cell glycocalyx. The study included 27 patients with ANMDARE, 11 with viral meningoencephalitis, and 22 control participants, and the results showed that serum and CSF levels of CD138 were significantly increased in patients with ANMDARE. After 3 to 6 months, their CSF CD138 levels were significantly decreased. Decreases in CD138 levels were associated with an improvement in the clinical outcome measured by the mRS. The findings suggest that a high level of CSF CD138 is associated with inflammation and poor prognosis.

In a recent major review of autoimmune encephalitis (comprising multiple mechanisms, including ANMDARE), Broadley and colleagues reviewed 44 publications representing 2823 reported patients, of which 27 studies and 1566 cases were ANMDARE.12 Specifically pertaining to diagnosis for ANMDARE, and mindful of the emerging and somewhat varied research methodology in this area, the authors concluded that ANMDARE diagnosis was worse with delay in initiation of or lack of immunotherapy, altered level of consciousness at clinical presentation, and admission to ICU. Other clinical variables, such as older age, sex, status epilepticus at clinical presentation, and abnormal CSF and MRI studies, did not have significant prognostic value, while the impact of antibody titers, dysautonomia, and comorbid malignancy was uncertain.

Discussion and Concluding Thoughts

The literature illuminates some key points about clinical presentation, risk factors, prognostic factors, clinical workup, and treatment recommendations for recurrent ANMDARE. Although ANMDARE usually presents initially as an abrupt onset of psychosis with comorbid neurologic symptoms and/or systemic symptoms, recurrent episodes may present, in rare cases, as an isolated change in mood or behavior (eg, delusional thinking, mood disturbances, aggression).

Risk factors for ANMDARE recurrence include presence of a tumor, lack of immunotherapy in the treatment of the initial encephalitis episode, and an increased CSF antibody titer compared with baseline. Poor prognostic factors include later initiation of treatment (more than 4 weeks after initial onset of symptoms) and ICU admission.

Many possible prognostic biomarkers are still under study, but some are at least partially understood. A normal EEG background, epileptic discharge, polymorphic delta rhythm, and diffuse beta activity are associated with a shorter hospital stay and good long-term prognosis, but abnormal EEG readings (eg, EDBs) have no clear correlation with the final clinical outcome. The ACS (age, disturbance of consciousness, and slow waves on EEG) score may be valuable in predicting the early-stage prognosis. The NNEG score may be used to predict the functional status after 1 year, but not the ultimate clinical outcome. Recovery can take more than 18 months. Patients experiencing recurrent episodes should undergo proper clinical workup to minimize the risk of further recurrence and improve prognosis.

For recurrent cases of ANMDARE, a detailed workup should be completed (Table 3).13,14 If the serum or CSF is positive for any onconeural antibodies, consider a full body PET scan to search for occult malignancy.1

Antibody titers should be interpreted with caution, as they may not be early or sensitive biomarkers. The improvement of symptoms has not
been found to be associated with a decline in antibody titers.1,2 Therefore, treatment decisions should be based more on clinical evaluations, rather than on antibody titers.3 For those who present with atypical clinical findings, such as the presence of a characteristic syndrome with negative serum antibodies or a discrepancy between serum and CSF antibodies, obtain comprehensive antibody testing (serum and CSF using 2 different techniques [eg, cell-based assay, brain immunohistochemistry, IIFT, ELISA, RIA, nanoliter immunomassay]).1,4 Collaboration between neurologists and psychiatrists is necessary to manage co-occurring neuropsychiatric symptoms.1 If the patient presents with rapidly progressive, refractory psychosis, and cognitive decline, consider brain biopsy.1

Treatment of first-episode and recurrent ANMDARE cases are similar. Both involve removal of circulating antibodies via tumor removal as well as plasma exchange, immunoadsorption, IVIGs, and/or immunosuppressors (eg, corticosteroids, azathioprine, methotrexate, mycophenolate mofetil).1 For unconfirmed cases of ANMDARE (eg, serum-only NMDAR antibody positivity without any other clinical abnormality), treatment with immunotherapy is not recommended and should be reviewed on a case-by-case basis by a team of neurologists and psychiatrists.1 For those who do not respond to first-line therapy with IVIG, plasma exchange, or high-dose corticosteroids, second-line immunotherapy with rituximab, cyclophosphamide, or both can significantly improve the outcome and decrease the frequency of relapses.2

In addition to immunomodulation, psychotic symptoms should be specifically managed. For the treatment of agitation, avoid high-potency antipsychotics (eg, haloperidol, risperidone) as they can worsen motor symptoms.2 Instead, use low-dopa- mine receptor blocking second-generation antipsychotics, starting at low doses and up-titrating slowly.3 Highly sedating medications such as zuclopenthixol, chlorpromazine, valproic acid, and benzodiazepines have anecdotally been useful for psychiatric symptoms,1 particularly benzodiazepines for catatonia and unclear cases of psychosis or aggression.1 ECT can be helpful for immediate symptom control.1 After the patient’s recovery from the ANMDARE episode, obtain their baseline serum and CSF titers to monitor for possible relapses; of the 2, the CSF titer is a more reliable indicator of new-onset relapse. Nevertheless, clinicians should base their treatment decisions more on clinical evaluation, rather than antibody titers, as the relationship among CSF antibody titer, prognosis, and relapse is still being studied.1

Monitoring for recurrence is lifelong, as ANMDARE episodes can reoccur months to years after initial onset. Further randomized controlled trials are needed for a universal consensus on management of ANMDARE. Dr Li is a recent graduate of Texas A&M College of Medicine and has recently joined the Texas A&M Psychiatry Residency Program in Bryan, Texas. Dr Bourgeois is chair, Department of Psychiatry, Baylor Scott & White Health, Central Texas Division, and clinical professor of medical education, College of Medicine, Texas A&M University Health Science Center, Temple, Texas.

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

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INGREZZA® (valbenazine) capsules are indicated for the treatment of adults with tardive dyskinesia.

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

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

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

QT Prolongation
INGREZZA may prolong the QT interval, although the degree of QT prolongation is not clinically significant at concentrations expected with recommended dosing. In patients taking a strong CYP3D4 or CYP3A4 inhibitor, or who are CYP3D4 poor metabolizers, INGREZZA concentrations may be higher and QT prolongation clinically significant. For patients who are CYP3D4 poor metabolizers or are taking a strong CYP3D4 inhibitor, dose reduction may be necessary. For patients taking a strong CYP3A4 inhibitor, the dose of INGREZZA should be reduced to 40 mg once daily. INGREZZA should be avoided in patients with congenital long QT syndrome or with arrhythmias associated with a prolonged QT interval. For patients at increased risk of a prolonged QT interval, assess the QT interval before increasing the dosage.

PARKINSONISM
INGREZZA may cause parkinsonism in patients with tardive dyskinesia. Parkinsonism has also been observed in patients treated with other VMAT2 inhibitors. In 5 placebo-controlled clinical studies in patients with tardive dyskinesia, the incidence of parkinson-like adverse events was 3% of patients treated with INGREZZA and <1% of placebo-treated patients. Postmarketing safety reports have described parkinson-like symptoms, some of which were severe and required hospitalization. In most cases, severe parkinsonism occurred within the first 2 weeks after starting or increasing the dose of INGREZZA. Associated symptoms have included falls, gait disturbances, tremor, drooling, and hypokinesia. In cases in which follow-up clinical information was available, parkinson-like symptoms were reported to resolve following discontinuation of INGREZZA therapy. Reduce the dose or discontinue INGREZZA treatment in patients who develop clinically significant parkinsonism.

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

• Hypersensitivity
• Somnolence
• QT Prolongation
• Parkinsonism

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

Variable and Fixed Dose Placebo-Controlled Trial Experience
The safety of INGREZZA was evaluated in 3 placebo-controlled studies, each 6 weeks in duration (fixed dose, dose escalation, dose reduction), including 445 patients. Patients were 26 to 84 years of age with moderate to severe tardive dyskinesia and had concurrent diagnoses of mood disorder (27%) or schizophrenia/schizoaffective disorder (72%). The mean age was 56 years. Patients were 57% Caucasian, 39% African-American, and 4% other. With respect to ethnicity, 26% were Hispanic or Latino. All subjects continued previous stable regimens of antipsychotics; 85% and 27% of subjects, respectively, were taking atypical and typical antipsychotic medications at study entry.

Adverse Reactions Leading to Discontinuation of Treatment
A total of 3% of INGREZZA treated patients and 2% of placebo-treated patients discontinued because of adverse reactions.

Common Adverse Reactions
Adverse reactions that occurred in the 3 placebo-controlled studies at an incidence of ≥2% and greater than placebo are presented in Table 1.

Table 1: Adverse Reactions in 3 Placebo-Controlled Studies of 6-week Treatment Duration Reported at ≥2% and >Placebo

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>INGREZZA (n=209) (%)</th>
<th>Placebo (n=183) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>10.9%</td>
<td>4.2%</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Articulatory effects (dry mouth, constipation, disturbance in attention, vision blurred, urinary retention)</td>
<td>5.4%</td>
<td>4.9%</td>
</tr>
<tr>
<td>Balance disorder (fall, gait disturbance, dizziness, balance disorder)</td>
<td>4.1%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Headache</td>
<td>3.4%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Akathisia (akathisia, restlessness)</td>
<td>2.7%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>2.6%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Nausea</td>
<td>2.3%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Musculoskeletal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Artralgia</td>
<td>2.3%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

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

Other Adverse Reaction Observed During the Premarketing Evaluation of INGREZZA

Dose-related increases in alkaline phosphatase and bilirubin, suggesting a potential risk for cholestasis.

Dose-related increase in alkaline phosphatase and bilirubin, suggesting a potential risk for cholestasis.

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

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

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

Skin and Subcutaneous Tissue Disorders: rash

DRUG INTERACTIONS
Drugs Having Clinically Important Interactions with INGREZZA

Table 2: Clinically Significant Drug Interactions with INGREZZA

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Interaction</th>
<th>Prevention or Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoamine Oxidase Inhibitors (MAOIs)</td>
<td>Concomitant use of INGREZZA with MAOIs may increase the concentration of monamine neurotransmitters in synapses, potentially leading to increased risk of adverse reactions such as serotonin syndrome, or attenuated treatment effect of INGREZZA.</td>
<td>Reduction may be necessary. For patients taking a strong CYP3D4 inhibitor, INGREZZA concentrations may be higher and QT prolongation clinically significant. For patients who are CYP2D6 poor metabolizers, INGREZZA concentrations may be higher and QT prolongation clinically significant. For patients who are CYP2D6 poor metabolizers or are taking a strong CYP2D6 inhibitor, dose reduction may be necessary. For patients taking a strong CYP3A4 inhibitor, the dose of INGREZZA should be reduced to 40 mg once daily. INGREZZA should be avoided in patients with congenital long QT syndrome or with arrhythmias associated with a prolonged QT interval. For patients at increased risk of a prolonged QT interval, assess the QT interval before increasing the dosage.</td>
</tr>
<tr>
<td>Strong CYP3A4 Inhibitors</td>
<td>Concomitant use of INGREZZA with strong CYP3A4 inhibitors increased the exposure (Cmax and AUC) to valbenazine and its active metabolite compared with the use of INGREZZA alone. Increased exposure of valbenazine and its active metabolite may increase the risk of exposure-related adverse reactions.</td>
<td>Reduce INGREZZA dose when INGREZZA is coadministered with a strong CYP3A4 inhibitor.</td>
</tr>
<tr>
<td>Strong CYP2D6 Inhibitors</td>
<td>Concomitant use of INGREZZA with strong CYP2D6 inhibitors decreased the exposure of valbenazine and its active metabolite compared to the use of INGREZZA alone. Reduced exposure of valbenazine and its active metabolite may reduce efficacy.</td>
<td>Reduce INGREZZA dose when INGREZZA is coadministered with a strong CYP2D6 inhibitor.</td>
</tr>
<tr>
<td>Strong CYP3A4 Inducers</td>
<td>Concomitant use of INGREZZA with a strong CYP3A4 inducer decreased the exposure of valbenazine and its active metabolite compared to the use of INGREZZA alone. Reduced exposure of valbenazine and its active metabolite may reduce efficacy.</td>
<td>Reduce INGREZZA dose when INGREZZA is coadministered with a strong CYP3A4 inducer.</td>
</tr>
<tr>
<td>Other</td>
<td>Concomitant use of INGREZZA with other drugs may increase the risk of exposure-related adverse reactions.</td>
<td>Dose adjustment of valbenazine may be necessary.</td>
</tr>
</tbody>
</table>

Other Adverse Reactions Observed During the Premarketing Evaluation of INGREZZA

Dosing adjustment for INGREZZA is not necessary when used in combination with substrates of CYP1A2, CYP2B6, CYP2C8, CYP2D6, CYP2C19, CYP2D6, or CYP3A4/5 based on in vivo study results.

OVERDOSAGE

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

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

INFORMATION FOR PATIENTS

Stated as Operating a Motor Vehicle or Operating Hazardous Machinery
Until they know how they will be affected by INGREZZA, patients should not perform activities requiring mental alertness such as operating a motor vehicle or operating hazardous machinery.

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

For further information on INGREZZA, call 84-INGREZZA (844-467-7902).

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San Diego, CA 92130

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THE SIMPLE CHOICE
FOR YOUR PATIENTS WITH TARDIVE DYSKINESIA (TD)

NOW AVAILABLE
60 mg Capsule

ONLY INGREZZA OFFERS ALL THE EASE OF:

- One capsule, once daily
- Effective dosing options
- No titration required
- Taken any time of day
- Taken with or without food

Give your patients all the ease of INGREZZA. See more at INGREZZAHCP.com/Dosing

Important Information

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WARNINGS & PRECAUTIONS (continued)

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

ADVERSE REACTIONS

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

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

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