This Is the Water
The Social Determinants of Mental Health and the Future of Psychiatry

By Kenneth S. Thompson, MD; and Allan Tasman, MD

The social determinants of mental health surround us. You only need to take a look around to see them. For instance, consider the following scenarios.

THE GUNSHOT THAT CHANGED HIM. “He shot my friend and his little boy as they were going into their house. I had just been walking with my friend when that guy walked right by me and shot them. I had just said goodbye on their front steps and was only about 20 feet away. My friend was a few years older, and I looked up to him. His son was 6. We both knew the guy who shot him, but I have no idea why it happened. I started feeling really depressed a few weeks later and made an appointment at the clinic.”

CONTINUED ON PAGE 5

COMMENTARY
The Goldwater Rule Is Fine, if Refined. Here’s How to Do it.

By Alan D. Blotcky, PhD; Ronald W. Pies, MD; and H. Steven Moffic, MD

The principle commonly known as the “Goldwater Rule” has been a part of the American Psychiatric Association’s (APA’s) Principles of Medical Ethics With Annotations Especially Applicable to Psychiatry since 1973. Known as “Annotation 7.3,” the Goldwater Rule prohibits psychiatrists from proffering diagnoses of current public and political figures who have not been professionally examined. More precisely, the annotation states, “… it is unethical for a psychiatrist to offer a professional opinion unless he or she has conducted an examination and has been granted proper authorization for such a statement.”

It is a seemingly straightforward statement that has not been substantially modified since its inception. However, in 2017 and 2018—in response to some psychiatrists’ concerns about the mental health of then-President Donald Trump—the APA Ethics Committee reaffirmed and tightened Annotation 7.3 by clarifying what is meant by “a professional opinion.”

CONTINUED ON PAGE 7
A chance to beat depression

Addressing the treatment of major depressive disorder in an entirely new way

The Reliance clinical research study is investigating a once-daily oral drug for people living with Major Depressive Disorder (MDD). Even with treatment, depression symptoms may persist. That is why Relmada Therapeutics is exploring a different approach to treatment with an investigational drug that may help to manage MDD through a novel mechanism targeting N-methyl-D-aspartate receptor (NMDAR) channels believed to be associated with MDD. If patients are not taking an antidepressant or are currently taking antidepressants but find that they are not fully managing their symptoms, one of the studies may be an option for them.

To learn more about these studies, visit RelianceStudies.com.
In Memoriam: Michael J. Hennessy Sr.

Psychiatric Times™ mourns the passing of Michael J. Hennessy Sr, chairman and CEO of MJH Life Sciences™. Hennessy was committed to improving health care and patients’ lives, as is seen throughout his career. Following his graduation from Rider University in 1970, he began his journey in medical publishing as a sales trainee, eventually advancing to the position of chief operating officer. In 1986, Hennessy became chief operating officer of Medical World Business Press, the company he co-founded and was eventually sold to a Boston-based venture capital firm.

Hennessy launched MultiMedia Healthcare, LLC, in 1993 and built a portfolio of award-winning clinical journals. In 2001, Freedom Communications, acquired MultiMedia HealthCare, LLC, now part of MJH Life Sciences™. Guided by the principles of innovation and entrepreneurial spirit and reflecting its founder’s dedication to improving quality of life through health care practice and education, MJH publishes a variety of integrated print and digital products on a range of topics in research and clinical medicine.

To build a comprehensive multimedia and education platform, Hennessy added other companies and capabilities to the MJH Life Sciences™ portfolio, including health care market research leader Healthcare Research & Analytics, respected journals Pharmacy Times® and The American Journal of Managed Care®, and the leading accredited continuing medical education company Physicians’ Education Resource®, LLC (PER®).

In 2019, MJH Life Sciences™ made its largest acquisition to date with the Healthcare and Industry Sciences divisions of UBM Medica, nearly doubling the size of the organization and adding legacy titles such as Psychiatric Times™ to an already impressive portfolio. This acquisition doubled the size of the organization and added legacy titles such as Psychiatric Times™ to an already impressive portfolio. This acquisition doubled the size of the organization and added legacy titles such as Psychiatric Times™ to an already impressive portfolio.

In late 2019, Hennessy elevated his role to Chairman while naming his son, Mike Hennessy Jr, to assume the leadership role of the organization and carry on the family legacy. Under Mike Jr.’s leadership, the company enhanced its global potential by entering into a long-term partnership with BDT Capital Partners, LLC, in November 2021.

Due to his broad business and educational experience, Hennessy’s counsel and insight had been sought out by several organizations, including his alma mater Rider University, where he served on the Board of Trustees and was elected to the executive committee. He also had a long record of service at the local level, where he was a strong advocate for veterans and environmental issues.

Hennessy’s true passion was his relationship with his wife, Patrice “Patti” Hennessy. After meeting her in college, Hennessy devoted his life to Patti and his family, raising 4 children. Hennessy was Patti’s rock as she bravely battled cancer for almost 10 years until her death in January 2020. Hennessy recently honored Patti by making a donation to Rider University to expand the Science and Technology Center at their alma mater. The Mike and Patti Hennessy Science and Technology Center is set to be completed in 2022.

Hennessy’s legacy and “family” mantra will live on through his children, their spouses, and his 10 grandchildren. He will be greatly missed by his family, friends, and his MJH Life Sciences™ family.
Hope for the New Year

John J. Miller, MD  Editor in Chief

Our tradition of making New Year’s resolutions is a good one, as we start the new year with hopefulness for improvements and growth for ourselves, humanity, and our planet. Unfortunately, all too often, by spring the resolutions are forgotten, as we fall into our usual routines and well-established habits. In psychiatry, our hope is often for a new treatment and ideally a cure for one of the many chronic and disabling conditions that are at the very center of our profession.

This past year, I read several articles as well as a book declaring that progress in psychiatric research is stagnant. These “glass half empty” opinions went so far as to claim that we have made no significant progress since the 1950s, when chlorpromazine and imipramine transformed psychopharmacology and were paradigm changes for our treatments for disorders such as schizophrenia and major depression. These writings went on to opine that all the research and drug development of the past 50 years have contributed very little to improved outcomes for our patients, and that all subsequent pharmacological agents developed are simply “me too” additions.

Working at a community mental health center, we serve a population that often has chronic symptoms, many of whom continue to decline in function over years and decades. Despite this, I hope to convince you that the glass is actually half full.

Psychiatry shares the challenges of all the other medical professions: many of the disease states that we treat have complex and multifactorial etiologies. These range from genetic vulnerabilities to intratranatal insults to environmental insults to results of suboptimal lifestyle behaviors to random accidents. Additionally, there is the simple fact that the great majority of us will die prior to the age of 100. Yet it is quite remarkable that the average life expectancy in the United States was 48 years in 1900 and had increased to 79 years by 2020. Many factors have contributed to this striking increase in longevity, including a dramatic decrease in infant and child mortality rates, vaccinations, antibiotics, improved health care on many fronts, access to good nutrition for many, and the numerous advances in science and technology. And, although the life expectancy statistics look promising, they do not factor in the many possible acute and chronic diseases that can affect quality of life and virtually every organ system, including the brain.

Medicine continues to make great strides in technology, drugs, and treatments to minimize the impact of these diseases on quality of life and, in some cases, to cure them. However, virtually every medical specialty has disease treatments that are at the very center of our planet. Unfortunately, and ideally a cure for one of the many chronic and disabling conditions that are at the very center of our profession.
states that persevere and, rather than being cured, are managed. Additionally, multiple factors—some modifiable and others unchangeable—will converge to accelerate or delay disease progression. Although the completion of the sequencing of all 3 billion base pairs in the human genome in 2003 was predicted to result in significant advances in diagnosing and treating all diseases, for the most part those advances did not happen.

According to the Centers for Disease Control and Prevention, the most common cause of death in the United States in 2019 continued to be heart disease.2 Despite the heart being a very straightforward and extensively studied organ—basically a pump—diseases of the heart continue to result in significant morbidity and functional impairment for many individuals. Does this mean that cardiology has failed as a specialty and no progress has been made? Of course not.

The human brain, the most complex organ known in the universe as of today, has many secrets awaiting our discovery. Over the past 100 years, we have merely begun our journey toward understanding the brain, and I posit that we have made great strides in treating psychiatric disorders, despite the likelihood that cures for many of these disorders, as for the heart, are far off in the future.

As I begin my 31st year as a practicing psychiatrist, I would like to welcome 2022 with reflections and hope for where we currently are as well as where we are heading in psychiatry.

Schizophrenia
I look forward to the time when the term schizophrenia disappears from our nosology. First named dementia praecox in 1886 by German psychiatrist Heinrich Schüle, this descriptor was popularized in 1893 by Emil Kraepelin, MD, who famously divided psychotic disorders into 2 subtypes: (1) dementia praecox and (2) manic depression, which we now call bipolar disorder. In 1908, Eugen Bleuler, MD, introduced the term schizophrenia, which translates from 2 Greek words as a split in the mind; this is the name that persists today.

A genetic vulnerability is well established, as well as effects from developmental challenges and environmental exposures. The savvy clinician will aggressively rule out many potential medical etiologies before settling on the diagnosis of schizophrenia, which will likely be a permanent label once etched into the patient’s medical record. A sampling of medical conditions that can mimic schizophrenia includes tertiary syphilis, seizure disorders, hyperthyroidism, Wilson disease, substance intoxication, medication toxicity, brain lesions, and anti-NMDA glutamate receptor autoimmune encephalitis, first reported in 2005.

It is thought-provoking that back in 1908 when Bleuler first described schizophrenia, most of these medical diagnoses had not been identified. Hence, these individuals would likely have received an incorrect diagnosis. A disturbing autobiography by a young New York Post journalist who, in 2009, developed an abrupt onset of manic, psychotic, delusional, and paranoid symptoms and was deteriorating with no response to usual treatment, revealed that she eventually received a diagnosis of anti-NMDA glutamate receptor autoimmune encephalitis, the 217th person diagnosed with this condition. She recovered completely following treatment with steroids, plasmapheresis, and intravenous immunoglobulin.3

What other as-yet undiscovered medical conditions are now lumped into the outdated diagnosis of schizophrenia? The half-full glass predicts that there are quite a few, but it may take years, decades, or even centuries to differentiate them. More disturbing to me is our lack of treatments for the negative and cognitive symptoms of schizophrenia. We have no pharmacological treatments for these common symptoms, which are ultimately the cause of disability and progressive functional impairment of individuals with schizophrenia. Why do we focus on searching for pharmacological solutions to these core symptoms? What if cardiologists treated patients with heart disease with only pharmacology? Individuals with heart disease maximize their functional improvement when they aggressively participate in cardiac rehabilitation, dietary modification, smoking cessation, daily exercise, and quality management of other comorbidities, and have increased social support.

Drawing upon this analogy, a major step forward has been the growing implementation of first-episode psychosis (FEP) programs in psychiatric clinics across the country. In 2009, the National Institute of Mental Health funded a study to investigate the benefits of aggressive and comprehensive treatment of individuals in their first psychotic episode. The study, Recovery After an Initial Schizophrenia Episode (RAISE), demonstrated that comprehensive early intervention for FEP improves symptoms and functioning superior to the usual standard-of-care models using 4 pillars of treatment (Table).4,5 We can call this half-full glass psychosis rehabilitation.

Finally, improved treatments with improved outcomes will happen as we further our understanding of the human brain, which will likely be a slow and arduous process. Our future treatment armamentarium for schizophrenia will likely include interventions about which we currently know nothing. As our learning progresses, our responsibility is to utilize all the tools that are available, and to give all patients full access to these treatments.

Treatment-Resistant Depression
It is well established that one-third of patients being treated for a major depressive episode will ultimately fall into the category of treatment resistant.6 Currently, when a patient’s initial presenting depression score improves by 50% or more with treatment, we classify this as a “response.” For patients whose depression score improves by 75% or more, we classify

Tender Fences
Richard Berlin, MD
– for JG
I’m revising my med student lecture notes on Models for the Doctor-Patient Relationship and the attitudes I want them to master: detached concern, therapeutic distance, good boundaries. But something is missing from my models, and I think back to a post-op dairy farmer too weak to milk the girls, and his neighbor who cares for them in a barn a mile away. For weeks they cry out for family and familiar stalls, and my patient cries with them. But as I get better, I missed my girls even more, and one night they escaped from my neighbor and wandered back home. He laughs, “It’s a good thing my neighbor has tender fences. Yes! Tender Fences, will be my model—barriers that create space for healing placed close enough to hear everyone’s cries of longing and love, a boundary strong enough to hold tight before it bends, yielding in time to get back home.”

Dr Berlin has been writing a poem about his experience of being a doctor every month for the past 23 years in PsychiatricTimes.com in a column called “Poetry of the Times.” He is instructor in psychiatry, University of Massachusetts Medical School, Worcester, Massachusetts.
them as “in remission.” For an individual who is severely depressed, a 50% improvement translates to continued significant depressive symptoms. Once a patient has completed and not responded to 2 adequate antidepressant trials of adequate dose and duration, the current consensus in psychiatry in the United States is that their depression is treatment resistant. This definition is arbitrary.

Depression is a complex emotional state, and the range of available treatments beyond pharmacology is immense. During my 30 years of practice, I have seen a steady decline in the use of nonpharmacological treatments, and a growing momentum that depression will improve once the right medication or combination of medications has been prescribed. The devolution toward this paradigm has been accelerated and supported by the policies of insurance companies reimbursing psychiatric providers for what they expect will be a 15- to 20-minute medication management visit. This is barely enough time to ask a few questions, continue or modify the medication regimen, order a lab or 2, review risks/benefits/adverse effects, and decide on follow-up. Oh, I almost forgot. This time theoretically also includes the extensive template-driven electronic medical record documentation. Realistically, there is no time to explore significant stressors or events, ask open-ended questions, or discuss nonpharmacological treatments that are viable and, at times, more appropriate options.

Our goal should always be full remission of depressive symptoms—as with the cardiologist, who ideally would treat heart disease back to an optimum cardiac output with no arrhythmias, normal blood pressure, and complete absence of any atherosclerotic plaques. However, just as many patients with cardiac issues continue to have significant heart disease even in the presence of optimal management, many patients with depression may have significant depressive symptoms once they are on an optimal medication regimen. In these settings, our goal is to maximize function and collaborate with the patient to educate them about and assist them in accessing all nonpharmacological treatments.

I treat a woman in her 40s who has had treatment-resistant depression for 9 years and has failed a long list of aggressive pharmacological trials. Recently, her daughter and only child informed her that she was pregnant and that my patient was going to be a grandmother. This news improved my patient’s chronic depressive symptoms significantly more than my 9 years of pharmacological trials. If our patients’ treatment-resistant depression coexists with significant psychosocial stressors, recent unpleasant major life changes, or a history of chronic abuse and trauma that began in childhood, rethinking the treatment plan to include a broader array of interventions than medications may provide substantial benefit, or at the very least affirm the patient’s residual symptoms in the context of their life experiences.

The Human Genome

Much excitement followed the complete sequencing of the human genome in 2003. It was a remarkable accomplishment resulting from the convergence of scientific understanding, technological advances in sequencing DNA, generous funding, worldwide cooperation, and a heroic commitment by all the individuals who contributed to the Human Genome Project’s completion.

Initially, the hope was that this treasure trove of information containing the blueprint of the human organism would accelerate our research and treatment of many diseases. Although much has been learned, 18 years later there have been few actionable clinical advances. One shocking discovery early on was that only 2% of the entire human genome coded for proteins—the remaining 98% was initially referred to as “junk DNA.”

Our limited understanding at the time was that the purpose of DNA was to preserve the information required to construct the many proteins necessary for human life. Since that time, the term junk DNA has been renamed noncoding DNA, and it is likely that much of this DNA has functions that we are just beginning to understand.

We now know that a significant percentage of noncoding DNA is evolutionarily preserved just like essential proteins, which strongly suggests that these sequences play a necessary role in the preservation of our species. It is likely that our future understanding of noncoding DNA will contain novel approaches to treat the wide range of human disease and disorders. That glass keeps filling up with more water.

Epigenetics

Epigenetics is a rapidly advancing field that nicely complements genetics and allows for the turning on and off of genes depending on developmental or environmental factors. Genetics and epigenetics are the embodiment of the beauty and necessity of nature and nurture in understanding the inherent plasticity of our genome. Epigenetic modification of the human genome is yet another fertile area that will likely greatly contribute to our understanding of the complex human disorders schizophrenia and major depression. For the interested reader, 2 articles I authored in 2021 issues of Psychiatric TimesTM are devoted to this topic: “Exploring the Epigenetic Paradigm Shift” and “Epigenetics Collides with Pharmacogenomics.”

Neuroplasticity

Our growing understanding of the circuits of the human brain provides yet another opportunity to appreciate that, rather than being a propped organ at birth, which I was taught in the early 1980s, the brain has inherent neuroplasticity, allowing it to change to its environment. A drug-receptor interaction, a memory-activated neuron, or a meaningful psychotherapeutic insight may trigger a cascade of neurochemical processes that ultimately can result in elevated levels of brain-derived neurotrophic factor, which then directs a target protein such as the mammalian target of rapamycin to facilitate synaptogenesis. For drugs such as ketamine and esketamine, this process is one putative mechanism that may contribute to their rapidly acting antidepressant effect. Abdallah et al demonstrated that patients who responded to ketamine showed an increase in global brain connectivity in the cingulate, insula, and lateral prefrontal cortex.

Concluding Thoughts

As the new year begins, taking a moment to reflect on where we have been, where we are, and where we are going is a useful exercise. In our young field of psychiatry, much has happened since Bleuler introduced the term schizophrenia in 1908. Clinical psychiatry today is very different than the field I trained in during the late 1980s—with a potpourri of advances, frustrations, external intrusions, and setbacks. But alas, such is the history of science, medicine, and psychiatry. Our challenge is to keep that flame of hope and optimism burning brightly, and to continue our journey together toward greater understanding, increased global citizenship and cooperation, and a strong dose of humility.

REFERENCES


FROM THE EDITOR

JANUARY 2022
This is the Water
Continued from Cover

This is what the patient I (AT) was seeing, in consultation with his treating resident, told me when I asked him why he decided to come to our clinic. The resident said that the patient, who he had been seeing monthly for medical checks, met the DSM-5 criteria for major depression and did not meet the DSM-5 criteria for acute stress. Assuming the patient’s symptoms were due to grief, he had started the patient on antidepressants 3 months prior, but there was no improvement. As the patient was talking with me, I agreed that his symptoms met the criteria for major depression. But something in the way he was talking made me feel as if he was holding something back. I apologized for perhaps being presumptuous, as we had not met before, and asked if my feeling made sense to him. After a moment’s hesitation, he said, “Yes, there is something. I just keep thinking about what happened, and I feel guilty. I think about it all night and can’t sleep. I should have done something to keep him and his son from being killed.” He did have a stress disorder, and the mood changes were part of it.

READY TO MOVE ON. Not long ago, a patient who had been working hard on her recovery from trauma, depression, and opiate use came to see me (KST) and said, “I want to get a job. I want a real pay-check. But I’m afraid to apply. What will I do when they ask me about the big gaps in my résumé? I know they won’t hire me.”

What tools can I use during treatment to help her learn to confront the stigma and discrimination she faces? What resources might there be to help her find work?

LACK OF SUPPORT. I (KST) was part of a project that created a treatment and recovery program in a shelter. It was successful. People got better.

Unfortunately, the patients soon realized there was no housing available for them, and they felt overwhelming disappointment. They “got all dressed up and had nowhere to go.” My team and I were distraught that we could only find housing for 1 of 10 participants. There was just not enough affordable housing to go around.

NEED FOR ADVOCATES ON A LARGER, MORE POLITICAL SCALE. I (KST) recently had a call from a friend of mine who has decided to run for Congress. He wants to help the people in Pittsburgh who have been left behind by the economy and further injured by the pandemic. He knows that 20% of the children in the district live in poverty. He knows about the deaths of despair due to opiates, suicide, and alcohol—the wages of deindustrialization. He wants to do the critical things necessary to improve our region’s health and well-being. What does he need to think about?

All of these scenarios present a number of questions. How did that resident—a very good one—miss a key emotional aspect of his patient’s world? How do we help people deal with the impact of stigma and other kinds of discrimination? How did we lose sight of the fact that people who are homeless need housing and that unemployed people want jobs? How often do we think about the importance of eliminating child poverty for the mental health of future generations? What in our psychiatric training and practice prepares us to really offer meaningful public policy advice that will equitably promote physical health, mental health, and well-being?

Where Has the Social in Biopsychosocial Been?

Should these questions come as a surprise to us? Of course not. Although science and experience have long made clear that social factors are a significant determinant of mental health and illness (as well as physical illness), we have often assumed there is little that we, as psychiatrists, can do about them. This has been particularly true for the last 40 years, with the rise of biological psychiatry and reaction against the social activism of the 1960s. It has resulted in omitting key aspects of the social in the biopsychosocial approach to psychiatric practice. This, in turn, has resulted in an inadvertent imprinting in our training programs and psychiatric practice with the belief that because there is little we can do about those factors at the societal level, there is little reason to address them with our patients, in our profession, or with society.

Rediscovery

But what if it’s not true that there is little we can do? What if we just haven’t found the most productive ways to act on behalf of our patients and the society in which we all live? Fortunately, in part due to the events of the past 2 years, the field has been thinking harder about this challenge. Our scientific evidence and our experience have made abundantly clear that psychiatric challenges are not randomly distributed among people. We now know that genetics plays a role. We also know that social identity and the experiences and exposures that constitute it plays a role—it is the water in which we swim.

Findings from innumerable studies in medical and psychiatric epidemiology have demonstrated a clear stepwise gradient at the population level between the burden of physical and psychiatric disorder and social class. Data from other studies have demonstrated how rates of disorders and treatments vary inequitably by age, geography, gender, sexual identity, disability, and race. These findings have brought a renewed focus on these experiences and exposures in a process we might compare to the efforts to map the genome.

In this regard, the work of Ruth S. Shim, MD, MPH, and Michael T. Compton, MD, MPH, and their colleagues stands out (Figure). Their 2015 book, The Social Determinants of Mental Health,1 incorporates years of study that directs our attention to the social determinants of general health and well-being. In the book, Shim and Compton outline some of the critical elements we must consider to

FIGURE. 16 Categories of Social Determinants of Mental Health, in 4 Broad Buckets

- Adverse childhood experiences
- Discrimination or social exclusion
- Exposure to violence
- Criminal justice involvement

Highly detrimental US societal problems

- Adverse built environment
- Neighborhood disorder
- Pollution
- Global climate change impact

Immediate and global physical environment

- Low educational attainment
- Unemployment or job insecurity
- Poverty and income inequality
- Neighborhood poverty

Socioeconomic status and opportunities for accruing wealth

- Basic needs in terms of housing, food, transportation, and health care

- Housing instability
- Food insecurity
- Poor inequality
- Poor access to transportation
- Poor access to health care


Merrill Rotter, MD, & Michael T. Compton, MD, MPH
better understand the social determinants of mental health in a way that is thorough, if not exhaustive. They include issues such as discrimination and adverse life experiences including exposure to violence, poor education, neighborhood deprivation, housing, unemployment, and more. They describe the impact of each of these on mental health with critically important ideas about how to address them at the clinical, public health practice, and policy levels.

Just as crucial as this new understanding of the problem is the growing willingness to act on it, fueled by a desire for social justice and to ensure that all people can thrive. Although distress over inequitable treatment on account of race, class, and gender has been around for a long time, only recently has the focus shifted to the much more ambitious desire to minimize, or ideally eliminate, inequities in the health status of different populations. The goal of achieving health equity goes far beyond that of ensuring health care for all. It reflects the growing awareness that health care has only a limited role in the production of health. This new pursuit of health equity requires a keen focus and action on the social determinants of mental health and well-being.

How can we do this? Where do we begin to enhance psychiatric training and practice to incorporate these issues? How can we better address the basic needs patients bring to us in practice? How can we develop a public health approach to mental health and create and implement primary prevention interventions? How can we begin to understand how social policies affect mental health, and where can we learn about and practice public policy development and implementation? Answering these questions will involve a sustained major effort throughout our profession.

We know that our largest professional organizations have withdrawn from addressing these issues, perhaps responding to harsh criticism of our social activism in the 1960s and 1970s. This moment, however, is different. If the events of the last decade—especially in the past 2 years—have taught us anything, it is that, as practicing psychiatrists, we cannot stick to narrowly defined “medical necessity.” We cannot take care of people and expect the world in which they live to take care of itself.

We need to know enough about their world to understand the challenges they face and address those during treatment. We have to learn what we can do to make that world a better place for them to be. And it goes beyond this. It is not just about our patients. It also includes the people who are not our patients (yet). We need to do all we can to help prevent psychiatric disorders and to equitably promote mental health and well-being. Of course, we cannot do this alone. We will need help from each other and from our whole society.

Moving Forward

To accomplish this, our profession must lead the charge. Not only do we have the knowledge that requires action, we also have a social position that demands it. As a group of privileged professionals, psychiatrists live very well in our current social structure. We certainly earn it, but much of our income results in part from the suffering our society generates. To not recognize and respond to this fact risks making us complicit with the inequities we see every day.

Fortunately, our largest and most important professional organization has, although belatedly, started stepping up. Vivian B. Pender, MD, president of the American Psychiatric Association (APA), has initiated the special Task Force on the Social Determinants of Mental Health. This group’s charge is to help catalyze action on the goals addressed in a position paper regarding social determinants endorsed by the APA Board of Trustees and Assembly in 2018 (Table).

While, to date, there has been little action to implement the positions approved in 2018, task force work groups are currently considering how the APA can better promote and implement the positions approved by the board of trustees 3 years ago.

To ensure that the work of the task force does not become just another paper on a shelf, the task force submitted a proposal to the APA board to fund a full-time staff director position so that our most important professional organization can more effectively focus on the social determinants of mental health. This proposal was rejected as premature by the APA budget committee in November 2021, and the future for APA action in this regard is not known as we write this column.

Author David Foster Wallace famously observed that just as fish do not recognize the water in which they swim, people often have little awareness of the world in which we all inhabit. It is too close—for example, taking a great deal of effort and time to gain enough perspective to see the incredibly complex social aspects of our world and to learn how they can be shaped for ourselves and others.

It is our hope that, as you read this, you have already learned that the APA—the flagship organization of our profession—has better understood the water around us and has not missed the boat to begin a new journey toward more effective training, practice, and advocacy regarding the social determinants of mental health.

Dr Thompson is medical director and founder of the Pennsylvania Psychiatric Leadership Council and former medical director of the Center for Mental Health Services at the Substance Abuse and Mental Health Services Administration. Dr Tasman is emeritus John J. and Ruby B. Schwab Endowed Chair in Social, Community and Family Psychiatry and a professor at the University of Louisville School of Medicine, past president of the APA, and editor emeritus of Psychiatric Times. Both authors are members of the APA Task Force on the Social Determinants of Mental Health, but the perspectives and opinions expressed in this article are their own and not necessarily those of the task force.

REFERENCES

<table>
<thead>
<tr>
<th>TABLE. THE APA’S POSITION STATEMENT ON SOCIAL DETERMINANTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>The American Psychiatric Association’s “Position Statement on Mental Health Equity and the Social and Structural Determinants of Mental Health” states:</td>
</tr>
<tr>
<td><strong>The American Psychiatric Association:</strong></td>
</tr>
<tr>
<td>▶ Supports legislation and policies that promote mental health equity and improve the social and structural determinants of mental health and formally objects to legislation and policies that perpetuate structural inequities.</td>
</tr>
<tr>
<td>▶ Advocates for the dissemination of evidence-based interventions that improve both the social and mental health needs of patients and their families.</td>
</tr>
<tr>
<td>▶ Urges health care systems to assess and improve their capabilities to screen, understand, and address the structural and social determinants of mental health.</td>
</tr>
<tr>
<td>▶ Supports medical and public education on the structural and social determinants of mental health, mental health equity, and related evidence-based interventions.</td>
</tr>
<tr>
<td>▶ Urges medical school and graduate medical education accreditation and professional bodies to emphasize educational competencies in structural and social determinants of mental health and mental health equity.</td>
</tr>
<tr>
<td>▶ Urges psychiatry residency training directors and other psychiatric educators to use systematic approaches to teaching about structural and social determinants of mental health.</td>
</tr>
<tr>
<td>▶ Supports the training of psychiatrists, in graduate and continuing medical education, in best practices to address the structural and social determinants of mental health and promote health equity.</td>
</tr>
<tr>
<td>▶ Advocates for increased funding for research to better understand the mechanisms by which structural and social determinants affect mental illness and recovery and to develop new evidence-based interventions to promote mental health equity.</td>
</tr>
</tbody>
</table>

PSYCHIATRIC TIMES™
www.psychiatrictimes.com

JANUARY 2022
Making a diagnosis, for example, would be rendering a professional opinion. However, a diagnosis is not required for an opinion to be professional. Instead, when a psychiatrist renders an opinion about the affect, behavior, speech, or other presentation of an individual that draws on the skills, training, expertise, and knowledge inherent in the practice of psychiatry, the opinion is a professional one. Thus, saying that a person does not have an illness is also a professional opinion.4

Since 1973, the Goldwater Rule has served its original purpose of keeping psychiatrists and other mental health professionals from making flippant, speculative, and/or unverifiable inferences about the mental health of (living) public and political figures. In our view, the Goldwater Rule’s basic rationale is correct. However, ethical guidelines are not meant to remain static and fixed. Over years or decades, provisions may need to be revised or at least further delineated. Such is the case, in our opinion, with respect to the Goldwater Rule.

According to the APA’s Principles of Medical Ethics With Annotations Especially Applicable to Psychiatry, “A physician shall recognize a responsibility to participate in activities contributing to the improvement of the community and the betterment of public health.” Accordingly, there needs to be acceptable and ethical ways for psychiatrists and other mental health professionals to opine about political and public figures on behalf of the public’s well-being and society’s greater good. Serving society and the public health does not occur in a clinician’s office—it often requires reaching out to the public via the media. And because of explosive advances in technology, the media now include cable television, radio, print, internet websites, audio recordings, video recordings, tweets, podcasts, and so many more platforms. It is through these various media outlets that psychiatrists and other mental health experts can responsibly influence and improve the community and public health.

The Times, They Are A-Changin’

Back in 1973, when Annotation 7.3 was adopted, only a handful of media outlets were available. Today, the media are vast and ever-present, and an expert’s opinions can be seen and heard almost instantaneously throughout the world. Having a clear understanding of what is ethically acceptable will make interacting with the media more comfortable and effective.

The public is bombarded with mountains of information and opinions on a minute-by-minute basis. Unfortunately, much of the material is inaccurate and even harmful. Misinformation and disinformation regarding mental health and mental illness now abound. Who better to provide accurate and helpful knowledge than mental health experts, whose education, training, knowledge, and expertise can be brought to bear on the prevailing public and social issues of the day?

Refining the Goldwater Rule

By necessity, then, the Goldwater Rule needs to be better defined, clarified, and expanded so that it provides a clear direction for psychiatrists who want to interact ethically with the media. Building on a 2016 article by Pies,5 we propose that the following 5 categories of professional discussion and opinion be deemed ethical and specifically incorporated into a revised Goldwater Rule.

1 A professional opinion may explain the positive and negative effects of a specific mental disorder in a hypothetical public or political figure. For example, psychiatrists could explain how antisocial or narcissistic personality disorder might manifest in a hypothetical elected public official.

2 A provisional diagnosis or professional opinion regarding a (deceased) historical figure may teach us something about current public or political figures. An example would be a discussion of Abraham Lincoln’s depression or Richard Nixon’s well-documented alcohol abuse and paranoia.6,7

3 A professional discussion regarding a living public or political figure may focus exclusively on publicly observable behaviors or behavior patterns that, in principle, might affect the person’s ability to perform their duties. This type of discussion would not proffer a diagnosis or reach a conclusion regarding the person’s fitness for duty, dangerousness, or ability to serve in a specific capacity. To illustrate, we offer 1 inappropriate and 1 appropriate response to a typical media-generated question:

“In my professional opinion, Congresswoman Young’s mood swings and intervals of abnormal speech and erratic, impulsive behaviors that have lasted for 2 to 3 days. A psychiatrist is asked by a newspaper reporter, “Doctor, can you comment on Congresswoman Young’s mood swings and erratic, impulsive behaviors? Could she have bipolar disorder, and would this render her unfit for the presidency?”

Inappropriate response: “In my professional opinion, Congresswoman Young’s obvious and extreme mood swings; emotional lability; rapid, pressured speech; and periods of irritability all point to a diagnosis of bipolar disorder. This condition, if left untreated, could well impair her ability to function in the role of US president.”

Appropriate response: “I have not evaluated Congresswoman Young, so I do not want to speculate on her condition or mental capabilities. When psychiatrists evaluate the behaviors you are describing, we consider a number of neuropsychiatric disorders in our differential diagnosis. For example, bipolar disorder can, indeed, be characterized by significant mood swings; emotional lability; rapid, pressured speech; and periods of irritability. But similar symptoms may be seen in several substance use disorders, such as methamphetamine use disorder, or in borderline personality disorder. Endocrine disturbances, such as abnormal thyroid function, or the periodic use of

4 A professional discussion may focus on the differential diagnosis of publicly observed behaviors or behavior patterns in relation to a current public or political figure. As in the previous example, a discussion could be provided by a mental health professional without diagnosing the person in question or opining on the person’s job fitness or dangerousness. Again, we provide an inappropriate and an appropriate professional response:

“Congresswoman Young” is running for president of the United States. Over the past 6 months, reports in the media have raised the question of manic-depressive illness or bipolar disorder. Reports in the lay press have cited Congresswoman Young’s extreme mood swings and intervals of abnormal speech and erratic, impulsive behaviors that have lasted for 2 to 3 days. A psychiatrist is asked by a newspaper reporter, “Doctor, can you comment on Congresswoman Young’s mood swings and erratic, impulsive behaviors? Could she have bipolar disorder, and would this render her unfit for the presidency?”

Inappropriate response: “In my professional opinion, Congresswoman Young’s obvious and extreme mood swings; emotional lability; rapid, pressured speech; and periods of irritability all point to a diagnosis of bipolar disorder. This condition, if left untreated, could well impair her ability to function in the role of US president.”

Appropriate response: “I have not evaluated Congresswoman Young, so I do not want to speculate on her condition or mental capabilities. When psychiatrists evaluate the behaviors you are describing, we consider a number of neuropsychiatric disorders in our differential diagnosis. For example, bipolar disorder can, indeed, be characterized by significant mood swings; emotional lability; rapid, pressured speech; and periods of irritability. But similar symptoms may be seen in several substance use disorders, such as methamphetamine use disorder, or in borderline personality disorder. Endocrine disturbances, such as abnormal thyroid function, or the periodic use of

5 Refining the Goldwater Rule

A provisional diagnosis or professional opinion regarding a (deceased) historical figure may teach us something about current public or political figures. An example would be a discussion of Abraham Lincoln’s depression or Richard Nixon’s well-documented alcohol abuse and paranoia.

6 A professional discussion regarding a living public or political figure may focus exclusively on publicly observable behaviors or behavior patterns that, in principle, might affect the person’s ability to perform their duties. This type of discussion would not proffer a diagnosis or reach a conclusion regarding the person’s fitness for duty, dangerousness, or ability to serve in a specific capacity. To illustrate, we offer 1 inappropriate and 1 appropriate response to a typical media-generated question:

“In my professional opinion, Congresswoman Young’s mood swings and erratic, impulsive behaviors? Could she have bipolar disorder, and would this render her unfit for the presidency?”

Inappropriate response: “In my professional opinion, Congresswoman Young’s obvious and extreme mood swings; emotional lability; rapid, pressured speech; and periods of irritability all point to a diagnosis of bipolar disorder. This condition, if left untreated, could well impair her ability to function in the role of US president.”

Appropriate response: “I have not evaluated Congresswoman Young, so I do not want to speculate on her condition or mental capabilities. When psychiatrists evaluate the behaviors you are describing, we consider a number of neuropsychiatric disorders in our differential diagnosis. For example, bipolar disorder can, indeed, be characterized by significant mood swings; emotional lability; rapid, pressured speech; and periods of irritability. But similar symptoms may be seen in several substance use disorders, such as methamphetamine use disorder, or in borderline personality disorder. Endocrine disturbances, such as abnormal thyroid function, or the periodic use of
corticosteroids can also produce signs and symptoms that may be mistaken for a mood disorder. Only a professional evaluation can determine what is actually going on with a particular person and what degree of impairment exists.”

A discussion of specific behaviors or behavior patterns attributed to a current public figure may be related to general categories of mental disorders. For example, the constellation of repeated lying; multiple legal infractions or arrests; interpersonal manipulativeness; and lack of empathy and concern for the rights of others could be discussed in relation to certain personality disorders (eg, narcissistic personality disorder, antisocial personality disorder). Absent a professional evaluation, care must be taken to avoid implying that the public figure in question fits one of these categories. Again, mental health professionals should refrain from making a diagnosis or speculating on the job fitness or dangerousness of a living public figure.

Conclusion

As can be seen, there are at least 5 ways in which psychiatrists and other mental health professionals can educate, inform, and provide guidance regarding public or political figures without violating the intent and spirit of the Goldwater Rule. To better understand and implement Annotation 7.3, it may be helpful to look at examples of the type we have provided to be presented and discussed in the revised annotation. Once revised, the Goldwater Rule could serve as a roadmap for psychiatrists and others who have a responsibility to improve the community and better the public health as they avoid the pitfalls of “armchair diagnosis.”

Finally, it must be emphasized that the Goldwater Rule does not limit psychiatrists or other mental health professionals as private citizens from expressing political views concerning a current situation, policy, or political figure. Health care professionals may always offer their opinions as concerned citizens without characterizing their views as professional judgments. Indeed, our representative democracy functions best when all its citizens are active, vocal, and articulate.

Dr Blotcky is a clinical and forensic psychologist in private practice in Birmingham, Alabama. He is also clinical associate professor in the Department of Psychiatry at the University of Alabama at Birmingham. Dr Pies is professor emeritus of psychiatry and lecturer on bioethics and humanities at SUNY Upstate Medical University. He is also clinical professor of psychiatry at Tufts University School of Medicine and Editor-in-Chief Emeritus of Psychiatric Times. Dr Moffic is an award-winning psychiatrist who specializes in the cultural and ethical aspects of psychiatry. A prolific writer and speaker, he received the one-time designation of Hero of Public Psychiatry from the Assembly of the American Psychiatric Association in 2002. He is retired from his tenured professorship at the Medical College of Wisconsin.

REFERENCES


5 Crypto Investing Rules for Busy Doctors » Jesse Proudmam & Logan Lutton

Cryptocurrencies can be complicated, to say the least. As a busy medical professional, you may not have time to research tokens or the nuances of this emerging asset class. As you consider investing in cryptocurrencies and other digital assets, you must understand and implement 5 Crypto Investing Rules for Busy Doctors.

1. Stick to your plan.
The crypto markets are very volatile, and you can expect many fluctuations. Although you cannot control the uncertainties and changes, you can dictate when and how much you invest. Be consistent, and focus on what you can control. Investors who chase good performance or run away from poor performance are less likely to be successful.

2. Don’t try to time the market.
It is difficult to know where cryptocurrency prices will move in the short term. Thus, the trick is to not worry about the short-term market. Focus on the long term and invest your money when you can. Do not waste time guessing where prices will go next; focus on investing over long-term horizons.

3. Diversify.
Diversification can reduce risk without hurting returns. This is a widely held ideal in the traditional investing world, but it has been slowly adopted in crypto. The idea is simple: Some assets go up in price, others go down. A balanced approach is a good option.

4. Invest in yourself while you invest in the market.
It can be useful and interesting to explore and learn as you invest. The technology behind crypto is fascinating, and learning about it can be done in small steps. Developing an appreciation for crypto’s innovations will give you the conviction to stick with the asset during volatile times.

5. Start early.
If you believe that crypto will be valuable over the long term, you benefit by getting started sooner rather than later. The best way to take advantage of the next wave of crypto excitement is to invest today.

If you are already investing or considering investing in crypto, these 5 tenets can serve as a foundation of your larger investment strategy.

Mr Proudmam is the cofounder and CEO of Makara as well as the co-founder of Strix Levisathan, a crypto hedge fund. Prior to his work at Makara and Strix Levisathan, he served as an IBM Distinguished Engineer, focused on blockchain and cryptography.

Makara Digital Corporation (“Makara”) is an investment adviser registered with the US Securities and Exchange Commission. Registration as an investment adviser does not imply a particular level of skill or training. Makara exclusively provides investment advisory services related to investing in cryptocurrencies and other digital assets. Makara is not a broker-dealer, exchange, custodian, or wallet provider, and is not intended for frequent trading activity. Investing in digital assets is highly speculative and volatile and Makara is only suitable for investors who are willing to bear the risk of loss and experience sharp drawdowns.

READ MORE:
TREATMENT RESISTANCE

The Current State of the Art and the Not Too Distant Future

Sheldon H. Preskorn, MD

The authors of the 3 articles in this Special Report have done a commendable job. Not only will you, the reader, benefit from reading these discussions, but, ultimately, so will your patients.

A few comments may help to put the issue of treatment resistance in perspective:

1. In these articles, the term treatment resistance is describing the illness the patient has rather than the patient being resistant. The importance of this distinction cannot be overstated. Caveat: There are patients who may decline treatment, but that is a different topic for a different time.

2. Patients do not fail treatments. Instead, treatments fail patients. This distinction also cannot be overstated.

3. Pharmacotherapy and psychotherapy are complimentary rather than antagonistic modalities. When explaining the relationship, I use the analogies of computer science in terms of hardware and software in computer science and/or orthopedic procedures (eg, casts) and physical therapy to explain the interrelationship between pharmacotherapy and psychotherapy. Psychiatry, like physical therapy, may be the only treatment the patient needs; however, it is rarely the case that a patient only needs pharmacotherapy without some form of psychotherapy, even if it is limited to supportive, educational psychotherapy.

4. There are 4 levels to diagnostic sophistication arranged like a pyramid. The first level is symptomatic diagnosis, which is what patients say when they present to a health care provider (HCP) (eg, “I have a headache.”). Moving up in the pyramid, the second level is syndromic, which is a cluster of symptoms and/or signs (i.e., physical findings), and the HCP may say to the patient: “You have a migraine headache.”). The third level up is pathophysiology, which is based on laboratory findings, such as elevated levels of norepinephrine in the bloodstream that causes the headache. The fourth level and top of the pyramid is pathobiology, which is the cause of the patient problem. In our example, a tumor, a pheochromocytoma, could be causing the high levels of norepinephrine which increased the patient blood pressure resulting in the headache.

As one can see, the higher the level of the diagnosis, the greater the understanding of the problem, what is causing the problem, and how to most effectively treat it. The lowest 2 levels of our pyramid are descriptive diagnoses, whereas the higher 2 levels are explanatory.

Presently, most psychiatric diagnoses are syndromic but we are moving to higher levels of understanding. That is good news for patients with treatment resistant psychiatric illnesses.

Dr. Preskorn is professor in the Department of Psychiatry and Behavioral Sciences at the Kansas University School of Medicine-Wichita. Over his 42-year academic medical career he has worked with more than 140 pharmaceutical, biotechnology, device, and diagnostics companies to bring their products to the market. He has been a principal investigator at the site level on all antipsychotic and antidepressants medications approved in the United States over a 25-year period of time. He has received grants/research support from or has served as a consultant, on the advisory board, or on the speaker’s bureau for Alkermes, BioXcel, Eisai, Janssen, Lyndard, Otsuka, Sunovion, and Usona Institute. All clinical trial and study contracts were with and payments made to The University of Kansas Medical Center Research Institute, a research institute affiliated with The University of Kansas School of Medicine-Wichita.

REFERENCES

Reducing Heterogeneity in Non–Treatment-Resistant and Treatment-Resistant Schizophrenia

Schiophrenia affects about 1% of the population and causes a tremendous burden on patients and families. Patients with schizophrenia present with diverse symptoms (ie, positive, negative, and cognitive), and the course and response to treatment varies widely. The basis of this heterogeneity is unknown but presumably results from a complex interaction of multiple genetic and environmental factors. To establish more homogeneous subpopulations, efforts have been made to use subtype based on clinical presentation or response to treatment, or by biomarkers derived from imaging, omics, or postmortem pathology (Figure). Due to the heterogeneity, subtyping approaches hold promise and should be considered when designing studies.

Definition of Response Subtypes

About 70% of patients respond at least reasonably well to treatment with standard antipsychotics (plus psychosocial interventions), and hence are considered to have non–treatment-resistant schizophrenia (non-TRS). However, up to 30% of patients do not respond to standard antipsychotic treatment and are therefore considered to have TRS, generally defined as a failed response to 2 approaches holding promise and should be considered when designing studies.

Table 1. Findings in Comparing UTRS and TRS

<table>
<thead>
<tr>
<th>UTRS is associated with:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Longer illness duration</td>
<td></td>
</tr>
<tr>
<td>Smaller thalamic volume</td>
<td></td>
</tr>
<tr>
<td>Lower prefrontal perfusion</td>
<td></td>
</tr>
<tr>
<td>Lower glutamate + glutamine in putamen</td>
<td></td>
</tr>
<tr>
<td>Higher anterior cingulate gyrus glutamate levels</td>
<td></td>
</tr>
<tr>
<td>Weaker network connectivity</td>
<td></td>
</tr>
<tr>
<td>Low-grade peripheral inflammation</td>
<td></td>
</tr>
</tbody>
</table>

Clinical Features

Analysis of clinical phenotype suggests that patients with TRS have an earlier onset of the disease than patients with non-TRS. Unlike non-TRS, the ratio of men to women with TRS is equal, although the extent to which this reflects a biological difference between non-TRS and TRS rather than the interaction of gender roles and age of disease onset remains to be determined. At the time of first diagnosis, patients who eventually develop TRS are more likely than future non-TRS patients to be inpatients, to require more medicine, and to spend more than 30 days in a psychiatric hospital. Cognitive functioning, and particularly verbal memory, is more impaired in patients with TRS than with non-TRS. TRS may also be more familial than non-TRS; first- and second-degree relatives of patients with TRS have an increased risk of developing schizophrenia compared with relatives of patients with non-TRS. The extent to which positive, negative, and cognitive symptoms associate with this different pattern of inheritance remains unclear.

Neurobiological Features

To understand the neurobiology of TRS, investigations have taken 2 general approaches. One is to determine the genetics of clozapine response, and the second is to identify genes and biological pathways most relevant to TRS. Initial pharmacogenetic studies of clozapine took a candidate gene approach and tended to focus on the major neurotransmitter systems implicated in the pharmacodynamics of clozapine and other antipsychotics. Response to clozapine was preliminarily associated with genetic markers linked to dopamine and serotonin receptors. However, these findings have not been consistently replicated, possibly due to variation in the criteria used to select subjects, inconsistencies in the definition of TRS, and ethnic differences among the populations under investigation, all in the context of small effect sizes.

Unbiased, noncandidate approaches to the neurobiology of schizophrenia provide an opportunity to identify novel pathogenic pathways. Because developing new antipsychotics based on fine-tuning the neurotransmitter profile of previously developed antipsychotics has not led to marked breakthroughs in clinical efficacy, this new approach is of critical importance. This is reflected in more recent pharmacogenomic approaches, using genome-wide association studies (GWAS) instead of data limited to markers associated with prespecified candidate genes. Findings suggest that patients with TRS, compared with patients with non-TRS, have higher polygenetic risk scores (an index of overall genetic risk of developing a disease), a higher frequency of disruptive mutations, and higher rates of chromosomal duplications and deletions. This approach has found an association between specific genomic loci and TRS including inter-alpha-trypsin inhibitor heavy chain 3/4 (ITIH3/4); calcium voltage-gated channel subunit alpha 1C (CACNA1C); and serologically defined colon cancer antigen 8 (SDCCAG8). Many of these studies have not yet been replicated, again likely a consequence of the small sample size, inconsistent inclusion criteria, and varying definitions of TRS.

As an alternative approach to pharmacogenomic studies of clozapine using GWAS, our laboratory examined gene expression in autopsied human brains from individuals with TRS (on clozapine at time of death) and non-TRS (on conventional antipsychotics at time of death). A number of specific genes were differently expressed, including the genes glutamate-cysteine ligase modifier subunit (GCLM), zinc finger protein 652 (ZNF652), and glycoprotein C (GYPC). Pathways associated with TRS included clathrin-mediated endocytosis, stress-activated protein kinase C-Jun-terminal kinase signaling, 3-phosphoinositide synthesis, and paxillin signaling, each providing potential leads in the search for new therapeutic targets.

Imaging Features

Imaging studies show relative frontal and temporal grey matter volume deficits in TRS, possible white matter tract disruption, and disruptions of functional connectivity, particularly in fronto-temporo-parietal grey matter. unwilling to prescribing clozapine due to concern about adverse effects. While clozapine can also be used in patients who have not responded to atypical antipsychotics, it is not without risk, and its use is associated with a higher risk of agranulocytosis.

“Delay in initiating clozapine treatment is associated with poorer outcomes, and potentially with adverse effects from exposure to excess doses of ineffective medicines.”
poral networks, with direct and indirect involvement of the thalamus.\textsuperscript{22-25} Perfusion measured by single-photon emission computerized tomography (SPECT) appears to be reduced in multiple brain regions in TRS and is partially corrected by clozapine; clinical improvement correlates with improved perfusion in the thalamus.\textsuperscript{13,22,27}

Further, treatment-resistant hallucinations correlated with increased cerebral blood flow measured by arterial spin label MRI in the temporal-parietal cortex.\textsuperscript{28} (18)F-FDOPA positron emission tomography studies detected higher striatal DA synthesis capacity in patients with non-TRS than in those with TRS and healthy control (HC) individuals, but no difference in DA synthesis capacity between TRS and HC.\textsuperscript{29} Elevated glutamate concentration in the anterior cingulate cortex was identified in the patients with TRS compared with non-TRS and HC,\textsuperscript{30} a finding that was subsequently replicated.\textsuperscript{31} The utility of these measures for determining which patients should receive clozapine remains to be determined.

**Differentiating UTRS and TRS**

To date, few studies separate TRS from UTRS, which is potentially a serious impediment to defining disease neurobiology, as these 2 forms of TRS may be pathologically and pathophysiologically distinct. The findings of the few studies that have directly compared TRS with UTRS, or UTRS with HC, are listed in Table 1. It is likely that these are fundamental to the illness and not a factor of disease progression because the majority of patients who develop TRS do so from the onset of symptoms,\textsuperscript{32} and the majority of patients with UTRS show limited improvement from the beginning of treatment with clozapine. So far, these findings remain preliminary and await replication. Using biochemical techniques, our laboratory has recently demonstrated increased protein insolubility, and potentially protein aggregation, in a subset of autopsied brains of individuals with schizophrenia.\textsuperscript{33} It is possible that this phenomenon, or related pathophysiological processes, may distinguish among non-TRS, TRS, and UTRS.

We performed a cross-sectional study to determine if there are differences in symptoms, cognitive functioning, or real-world functional capacity among non-TRS, TRS, and UTRS. Patients who responded to clozapine performed significantly better on a validated assessment tool of function, developed by Philip Harvey, PhD, and colleagues, consisting of computer simulations of banking at an ATM, purchasing a ticket, and obtaining a prescription refill, and on overall cognition as assessed by the Brief Assessment of Cognition in Schizophrenia. The cross-sectional design did not allow us to determine if patients who eventually responded to clozapine were as impaired as eventual nonresponders but improved on clozapine, or if they were less functionally impaired at the outset of clozapine treatment. This last question will be addressed in a longitudinal study of individuals beginning treatment with clozapine.

This study highlights the potential confounding of grouping UTRS with TRS in studies of disease phenotype, pathogenesis, and treatment response. It is possible, for instance, that some—or all—of the genetic and neurobiological differences reported between non-TRS and TRS is in fact driven by UTRS. Furthermore, our work on protein homeostasis abnormalities and protein insolubility suggests that pathological processes can be identified in a subtype of patients with clinical correlations subsequently determined and eventually, specific treatments designed (Figure).\textsuperscript{34} Taken together, the available data suggests that subtyping based on treatment response is a plausible approach to understanding the heterogeneous pathophysiological mechanisms related to schizophrenia. This is somewhat analogous to the past recognition that subtypes of psychiatric syndromes that strongly resemble idiopathic schizophrenia could be explained by infections (eg, syphilis), nutritional deficiency (eg, niacin), or substances (eg, chronic amphetamine abuse).

Historically, this type of reasoning has led to advances and specific treatments, as specific causes of psychotic syndromes—including syphilis, niacin deficiency, and chronic amphetamine abuse—were identified. TRS is one way to subtype patients, but other approaches using variability in physiological parameters, such as the Bipolar and Schizophrenia Network for Intermediate Phenotypes (BSNIP), or protein homeostats abnormalities, as we have shown, are other ways that this problem could be addressed.

**Recommendations for Treatment**

Although clozapine has been clearly established as the treatment of choice for individuals with schizophrenia who do not respond to 2 trials of a standard antipsychotic, or who have other specific indications, it is vastly underused. Based on the rate of treatment failure of conventional antipsychotics, the indication of clozapine for reducing the risk of suicide, the relatively low risk of neurological disorders with clozapine, and the potential value of the drug in ameliorating schizophrenia symptoms such as polydipsia, between 30% and 40% of US patients with schizophrenia should be receiving clozapine, whereas the actual rate is approximately 4%.\textsuperscript{35} Even for those receiving clozapine, the average delay from the point in time when clozapine would have been considered indicated is 48 months.\textsuperscript{36} Patients who might respond to clozapine are instead treated with multiple antipsychotics or high-dose antipsychotics. The undertreatment is likely a consequence of strict guidelines for prescribing clozapine that burden both clinicians and patients, and fear of adverse effects on the part of patient, family, and clinicians.

Unfortunately, our current understanding of the neurobiology of TRS and UTRS is insufficient to predict who will respond to clozapine and who will develop adverse effects. Delay in initiating clozapine treatment is associated with poorer outcomes, and potentially with adverse effects from exposure to excess doses of ineffective medicines. Clozapine adverse effects
Table 2. Resources for Prescribing Clozapine

■ American Psychiatric Association’s Severe Mental Illness Adviser Clozapine Center of Excellence
■ Clozapine Center for Help and Assistance for Maryland Prescribers-Intervention Outcomes Network Extension for Community Healthcare Outcomes (CHAMPION-ECO; currently being trialed in Maryland to educate prescribers on how to use clozapine and manage adverse effects)

TREATMENT RESISTANCE

SPECIAL REPORT

JANUARY 2022

www.psychiatrictimes.com

Pharmacological Management of Treatment-Resistant Anorexia Nervosa

For patients with AN who show signs of treatment resistance, the most common medication intervention is atypical antipsychotics. Although promising case reports, open trials, and chart reviews began appearing in the late 1990s, the controlled-trial literature on atypical antipsychotics in AN remains disturbingly limited, which is a testament to the notorious difficulties in recruiting and retaining patients with AN in medication trials. To date, there have been 8 randomized, placebo-controlled trials (RCTs) involving placebo groups. Only 1 of these involved more than 40 patients, and the total number of randomized patients in all trials was less than 350.13,14

**ONLY 13% TO 50% of patients are considered recovered 1 to 2 years posttreatment.**

20% TO 30% go on to develop a chronic and unremitting course of AN.4

Olanzapine is by far the most studied medication for AN, with 5 trials taking place between 2007 and 2019. All but 1 were considered positive, although the degree of benefit typically was small. Two trials involving use of quetiapine had mixed results, and 1 trial with risperidone was negative.15

In the closest thing to a landmark medication study in AN, Attia et al reported results of a relatively large, multisite RCT of olanzapine in adult outpatients in 2019.12 Five sites in North America randomized 152 patients to olanzapine or placebo during a 6-year recruitment period. The 16-week trial used a target olanzapine dose of 10 mg/d (mean, 7.77 mg/d), and investigators found a significant increase in weight for the olanzapine group versus placebo. However, the difference in weight gain (ie, 1 lb of body weight/month for a woman of average height) was modest between the groups; patients using olanzapine gained an average of approximately 1.5 lb of body weight/month. Weight restoration is the primary outcome in any AN trial, but use of a medication hopefully also will impact the powerful thought processes and psychiatric symptoms that drive the illness. Importantly, the authors reported that use of olanzapine showed "no significant benefit for psychological symptoms."12,14

Despite these limitations, expert articles and guidelines most likely recommend olanzapine as the antipsychotic of choice to treat AN, because so few RCTs have involved use of other medications. In our experience, a few types of patients may particularly benefit from olanzapine. For individuals who desire some degree of weight restoration but are struggling due to lack of appetite or drive to eat, olanzapine may provide improvement. In addition, patients with very high anxiety presenting more as fear than cognitive rigidity may benefit from the sedative-like properties of olanzapine.

However, there are substantial roadblocks to successful use of olanzapine for AN. The quality that led to early interest in and dominant study of olanzapine—its well-known propensity to cause weight gain—makes it unacceptable to the vast majority of patients with AN. At best, many of these individuals are ambivalent about weight gain, and even those who have accepted it as a necessary aspect of recovery frequently fear loss of control over the process. It is critical to understand that improvement in body image for AN patients can significantly lag weight restoration. If a medication adds weight but has little impact on thought process, the patient may experience an intolerable emotional state that greatly heightens the risks of nonadherence and resumption of weight loss.

With 14 atypical antipsychotics available for use in the United States, it is astonishing that so few have been studied in RCTs of AN. Given the highly complex and variable receptor-binding properties of this class, leading to clinically relevant heterogeneity—for example, some atypical antipsychotics are known to treat depression better than others—it is premature to conclude that atypical antipsychotics have only minimal benefit for AN based on results reported with use of 3 of the earlier medications. Lack of RCTs with newer, relatively weight-neutral antipsychotics, especially those having a somewhat different mechanism of action (eg, aripiprazole), may be a serious oversight.

Over the past decade, and with the 2019 olanzapine trial notwithstanding, nearly all additions to the literature on the use of atypical antipsychotics in patients with AN have involved aripiprazole. Five peer-reviewed articles from 4 different sites in 3 countries have described very interesting findings from case series and retrospective chart reviews.13,14 These reports often show benefit for weight gain, but most notably, they have included remarkably similar descriptions of an impact on thought processes related to AN, particularly the loosening of rigid and entrenched rules and distortions. Observations have included reduced eating-specific anxiety and distress; less rigid food choices; diminished obsessional thoughts about food, exercise, weight, and body image; and fewer eating disorder (ED) rituals. Additionally, many patients reported reduced symptoms of depression and non-ED–related anxiety, which will be discussed in the next section. Therefore, regardless of any direct impact on weight, aripiprazole may indirectly enhance weight restoration by improving cognition and thereby promoting a better response to psychological and dietary treatments. RCTs are needed to further investigate these findings.
What may account for this possible difference between olanzapine and aripiprazole in AN? Olanzapine—assumed with other current atypical antipsychotics, including quetiapine and risperidone—is a 5-HT2/D2 antagonist. Aripiprazole, in contrast, is a D1 and 5-HT1 partial agonist, meaning it acts differently at dopamine and serotonin receptors. Theoretical arguments have addressed how use of aripiprazole at lower doses (typically 1-5 mg/d, with occasional titration up to 10 mg/d) may facilitate learning and behavior change in individuals with AN.

For example, basic research has indicated that dopamine receptor stimulation may be beneficial in suppressing previous fears after extinction training. Moreover, neurobiological research suggests that AN is associated with heightened responsiveness in brain reward circuits, which may be due to a hypersensitive dopamine system. Aripiprazole may downregulate D3 receptor activity, which may improve brain function, reduce anxiety, and aid in the psychotherapeutic process.11,13,15

Additionally, almost all patients described in this research on aripiprazole use were being treated concurrently with antidepressants. In contrast, no RCT has formally studied atypical antipsychotic augmentation of antidepressants in AN. Although some RCTs allowed patients already on antidepressants to continue them, use was not systematic or evaluated, and the overall numbers were too small to yield meaningful results. We believe that, particularly for medications such as aripiprazole with known significant effects as augmenters, combination treatment may be 1 key to showing a more robust response in controlled trials. On a practical note, adherence also has improved with use of aripiprazole, because it often is better tolerated. Still, some patients encounter akathisia, which we have been able to minimize by initiating therapy with very low doses (eg, as low as 0.5 mg/d in some patients).

Impact of Psychiatric Comorbidities

AN is associated with high levels of comorbid conditions. More than 40% of individuals with AN have a lifetime comorbid anxiety or mood disorder, over 30% have an impulse control disorder, and about 27% have a substance use disorder.16 Recent data showed that individuals with AN had a 25% risk of receiving any noneating disorder diagnosis 2 decades after inclusion.17 Comorbid conditions have been associated with greater illness severity and mortality.1,19

Research on eating disorders traditionally has not focused on comorbidities, but new data highlight the need for treatment of those conditions. Whether eating disorder outcomes will be affected by treatment of comorbid psychiatric illnesses is uncertain, but improving quality of life and reducing suicide rates are similarly important goals.9,13,15,16

Few medications specific to AN have been approved by the FDA, yet affected patients frequently receive prescriptions for psychotropics.20,21 However, studies on pharmacological interventions in AN commonly have not been designed to discern whether individuals taking these medications had more severe illness or higher comorbidity than did others. Because depression and anxiety predict more negative treatment outcome in AN, and comorbid psychiatric disorders are associated with higher mortality among this patient population, use of medication to target these conditions is supported.12-14 Research may have to adapt and focus more on outcome measures that go beyond weight gain; these may include the study of quality of life, mood, and anxiety measures in relation to use of medical interventions. These measures are crucial in preventing weight loss and relapse after significant resources that involve a high level of care have been used for nutritional rehabilitation.

A recent patient with severe AN in our program also had severe, comorbid obsessive-compulsive disorder (OCD). She had many magical thinking–related obsessions that substantially limited her will to live and contributed to overwhelming major depressive disorder with suicidal ideation. The patient was treated with olanzapine to reduce distress and who had been on various antidepressant and anxiolytic medications, but she never received an adequately dosed trial of a selective serotonin reuptake inhibitor to treat OCD. During weight restoration, we initiated sertraline, which was titrated to 200 mg/d. After 4 months of treatment, the patient experienced significant relief from symptoms of OCD and could start participating in social activities. AN was still a significant struggle, but the patient experienced improvement in daily life activities and overall functioning.

Future Directions

While olanzapine has shown benefit for AN in RCTs, weight restoration tends to be minor, AN cognitions do not appear to improve significantly, and most patients are unaccepting of a medication known to cause weight gain. RCTs of additional atypical antipsychotics, especially those that have a somewhat different mechanism of action (eg, atypical antipsychotics), used alone and in combination with antidepressants are needed. Research into strategies to better treat psychiatric comorbidities in patients with this disorder may reduce treatment resistance. Finally, early investigations to treat AN and its comorbidities with novel biological treatments (eg, psilocybin, ketamine, cannabionoids, and neuromodulation techniques of repetitive transcranial magnetic stimulation and deep brain stimulation) are ongoing.12-15

Dr Trunko is an associate clinical professor of psychiatry at the University of California, San Diego, and medical director of the UCSD Eating Disorders Treatment and Research Program. Dr Frank is a professor in residence at psychiatry at the University of California, San Diego. Dr Schwartz is director of medical and clinical services at the UCSD Eating Disorders Treatment and Research Program, and clinical professor of psychiatry at the University of California, San Diego. Dr Kaye is the founder and executive director of the UCSD Eating Disorders Treatment and Research Program, and professor of psychiatry at the University of California, San Diego.

REFERENCES
CONVERSATIONS IN CRITICAL PSYCHIATRY

What Can Philosophy Learn From Madness? » Awais Aftab, MD

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

Wouter Kusters, PhD, is a Dutch linguist and philosopher. He is the author of Pure Waanzin (Pure Madness; Nieuwezijds; 2004) and Filosofie van de Waanzin (A Philosophy of Madness; Lemniscaat; 2014). An English translation of Filosofie van de Waanzin was published in 2020 by MIT Press with the title A Philosophy of Madness: The Experience of Psychotic Thinking (translated by Nancy Forest-Flier). Kusters works as an independent researcher, writer, teacher, and consultant in Gouda, Netherlands. For details, readers can explore his website at: https://kusterstext.nl/.

Pure Madness was based on Kusters’ own experience of a psychotic episode in 1987. It won a pair of important prizes in the Netherlands: the Van Helsdingen Award (2004) for the best work on the intersection of philosophy and psychiatry, and the Socrates Award (2005) for the best and most inspiring Dutch philosophy book of the year. After the publication of this book, Kusters made a professional switch, turning from academic linguistics to a career as an independent writer and researcher. He started studying again as an undergraduate philosophy student, during which time he published his second book on psychosis, Alone: Messages from the Isolation Cell (Lemniscaat; 2007). Shortly afterward, in the summer of 2007, he experienced his second episode of psychosis, which led to a psychiatric hospitalization, and this provided further impetus for him to continue his work on philosophy and madness. He finished his master’s thesis in philosophy in 2010, which formed the basis of an updated version of Pure Waanzin (Pure Madness; Lemniscaat; 2013) as well as of Filosofie van de Waanzin (A Philosophy of Madness; Lemniscaat; 2014. His books were a success in the Netherlands and met with widespread acclaim. The publication of the English translation of Filosofie van de Waanzin (A Philosophy of Madness: The Experience of Psychotic Thinking; MIT Press; 2020) has brought his work to the attention of the English-speaking world, and it has prompted a renewed debate on philosophical and phenomenological perspectives on psychosis as well as the relationship between philosophy and psychosis.

AFTAB: I think it would be prudent for us to begin with at least a few words regarding the nature of inquiry you are undertaking in A Philosophy of Madness, and how that relates to your own experiences of psychosis.

KUSTERS: My book is a philosophical treatise in the tradition of Montaigne’s Essays; in the vein of Nietzsche’s and Kierkegaard’s approaches to philosophy, and as a phenomenon called psychosis in psychiatric practice and theory. By stressing the experiential character of psychosis, which I have access to via my own memory, as well as via all kinds of reports and first-person narratives, the direction of my exploration is toward comparable experiences and their expressions. This brings us to all kinds of philosophical thoughts, bordering on reflections around religion, mysticism, and spirituality, but also to important themes of language, fiction, and nonfiction. For any psychiatrist educated a little beyond the mainstream medical illness, cure, and therapy narratives, it must be clear that my exercise brought me into the small but highly professional and well-informed tradition of phenomenological psychiatry.

AFTAB: You have argued that a philosophical investigation of psychosis provides a better and less prejudicial approach than many mainstream psychological and psychiatric accounts. What sort of prejudices do you have in mind?

KUSTERS: The main prejudice concerns the usual way of approaching psychosis as a negative or a lack and leaving it there. That is, seeing it purely as a deficit, a disorder, a nonfunctioning of some aspect of the mind/brain/body that is supposed to be well-functioning in the individual who is not psychotic. Take for example the idea, found in various kinds of mainstream accounts, that psychosis is some kind of thought disorder. Such a judgement implies that there is good, proper thought, and that psychotic thought can be sufficiently defined as a disturbance, a disordering of this normal, natural way of thinking. It may be said that the disorder is one of jumping too fast to conclusions, or a dysregulation of perceiving salience properly, or an inability to synthesize information coherently, or it is just being plainly illogical. All such approaches share the assumption (the prejudice) that psychosis can be sufficiently defined by what it is not.

The implication of such accounts is that the psychosis is just a disruption that should be suppressed and taken away in order to let the normal flow of experience run again uninterrupted. It is
In delusional insanity, paranoia, as they sometimes call it, we may have a diabolical mysticism, a sort of religious mysticism turned upside down. The same sense of ineffable importance in the smallest events, the same texts and words coming with new meanings, the same voices and visions and leadings and missions, the same controlling by extraneous powers; only this time the emotion is pessimistic, instead of consolations we have desolations; the meanings are dreadful; and the powers are enemies to life.

something is revealed about the nature of the world and our existence. Another approach might be more negative. In this approach, psychosis by itself does not tell us what reality is, but it throws our everyday epistemic complacency into disarray. We can no longer trust our sensory inputs, our perception of space and time, our social instincts, etc. and this provokes a state akin to Cartesian doubt, where we can no longer take our ordinary understanding of the world for granted. With some poetic license and oversimplification, perhaps I can refer to these positions as the epistemological and the mystical, respectively. Certainly, there can be all sorts of interesting combinations and variants of these approaches. Would you consider this to be a useful framing? If so, do you lean toward a particular position?

Kisters: That is a very illuminating framing indeed, and relates to the power of the negative. Let me comment on both positions and their relation to madness. In the original version of the Cartesian thought experiment, the one described by Descartes himself, a subject throws himself into full doubt, distrusts his senses, and searches within his own thought for a firm ground for existence, an undeniable truth, beyond all doubt. Descartes describes how in this process of radical doubt, everything is rejected because of its principled uncertainty, mutability, and transiency. The only thing that cannot be doubted, is that there is me, enveloped in a doubting process. And then from this elementary given, the famous rationalist adage follows: cogito, ergo sum (“I think, therefore I am”). In the dark nights of the mad soul, the individual with psychosis may have an analogous thought process, and they may end up in a kind of intellectual and existential despair, driven by radical self-doubt. But this despair may also take the form of an experience of perplexity about the undeniability and goodness of one’s own existence. The argumentative structure in Descartes’ texts shows similarities with the existential doubts the madman is in.

What is often forgotten in popular considerations of Cartesianism is that in building on cogito, ergo sum, Descartes goes on to prove the existence of God as well as reality, using arguments that are today seldom accepted as self-evident truths. Descartes draws the conclusion that from being able to think an utterly perfect being (God), we must conclude that this utterly perfect being exists, otherwise it would not be utterly perfect. Now, the madman may in myriad ways follow, mirror, and deviate from such ways of thinking, and may get fully lost in all kinds of imaginations that are very difficult for an outsider to understand. However, when we are aware of these philosophical problems and this basic scheme of Cartesian reasoning, we might come a little closer to some understanding.

Of course, there are also many differences between the Cartesian and the mad thought experiments. An important difference is that for Descartes this was simply a thought experiment, an epistemological exercise, but for the madman the radical doubt is a serious matter; he is drowning existentially, losing all firm ground, and desperately searching for an anchor. We might say indeed that Descartes performs an epistemological experiment, while, following the ideas of the Dutch psychiatrist and philosopher Antoine Mooij, the psychotic is involved in an ontological experiment.

Let’s look at mysticism in comparison. In the early days of Christianity, mysticism was an intellectual and theological way to argue, to contemplate, to pray, to envision, and eventually to experience awe at the greatness and the power of the Almighty God. Then there was no essential difference between mysticism, theology, and philosophy. It was only much later that mysticism became associated with visions in the West, in an epochal historical change in which visual hallucinations also became ascribed as a dominant characteristic of psychosis. Just as I stress the partially passive, experiential character of the active Cartesian doubt experiment, I view mysticism as a more active and intellectual undertaking than it is usually considered to be. The usual distinction made between active thought and passive perception (and their counterparts in psychopathology, delusions vs hallucinations) is too rigid, and it is in mad philosophy and philosophical madness that we see a continuing doubting of both, and a crossing of the separation between them, by way of the viability and flexibility of language signs and experience.
AFTAB: How do you approach the experience of delusions, which on the surface represent the antithesis of philosophical thinking? Instead of an ongoing grappling with a confusing reality, in the case of delusions we see a closing down of inquiry, resulting in what has traditionally been described as a fixed, false belief, unshakeable in the face of reasoning or contrary evidence. Would you say that perhaps it is only after the delusional force of the beliefs has dissipated that we can begin to philosophically understand the meaning of that experience?

KUSTERS: I think that delusions in the way you describe them here are only one side of the delusional story. Unlike many superficial cognitive accounts of delusion, I think that so-called delusions are better analyzed as reactions to an underlying, and temporally preceding, delusional mood, which is in fact also the position of most phenomenologists as well as psychoanalysts. A famous adage of the latter is that delusions are not the problem, but they are instead the first attempts to express and deal with another problem, of a quite different order. Nevertheless, I fully agree that a philosophical understanding, in the common understanding of this phrase, can only happen post festum. A self-understanding and a philosophical elaboration that is intelligible to others, communicable in common language, must handle and circumnavigate the seduction to remain trapped by the awe for the ineffable, both in its ecstatic as well as despairing forms. The paradox of any such understanding, including mine, is that with this understanding, the thing itself, the psychosis, is in danger of retreating beyond the horizon. And this same striving toward understanding may attract and provoke psychosis to rise up again from the invisible. I know that some readers of my book put it down, but then had to resist being drawn back toward that enigma.

AFTAB: In your interview with the webzine Mad in America, you say at one point: “Philosophy never promised you a rose garden, [and] neither do I. Furthermore, it could well be argued that there is some kind of antihuman tendency in extreme philosophical and psychotic thought. Both philosophy and madness may have intense ‘superhuman’ or ‘a-human’ powers that burn anything substantial, anything meaningful, away into a hole of nothingness. But, well, the interests of life are not necessarily those of philosophy.” Can you comment more on this misalignment between the interests of life and the interests of philosophy/psychosis?

KUSTERS: Most modern philosophy starts from and leads back to common-sense assumptions. Many are rooted in the Age of Enlightenment and have the overt values of modern society as their implicit background. They assume that what is argued by human thought, including the findings and results of philosophizing, are and should be beneficent for [human] life. We find that assumption under all kinds of moral and political philosophies, but also under so-called philosophy of psychiatry. However, it is not so obvious that philosophical thought should lead to beneficial effects on society or the individual.

There are a range of extreme critical philosophical views, such as views of ultraconservative, nationalistic, racist, anti-humanist, transhumanist, and even antinatalist nature. While some of these views are considered dangerous to society, they still remain sustained within a broadly defined space of reasons, although this may be contested by others. Some philosophical ideas go even further and have the paradoxical capacity to be self-undermining for the thinker who thinks them. They may be detrimental to what we usually consider the space of reason; they are contra [human] life. That is, they argue in quite sophisticated ways that not being is to be preferred over being. They use notions of emptiness, the void, and nothingness, not to draw positively flavored, so-called spiritual conclusions, but only to affirm annihilation, death, suicide, destruction, and [auto-]extinction. Such philosophies can be seen as a variety of nihilism—although this term refers to a much larger range of philosophies—important names such as Friedrich Nietzsche, of course, but also Emil Cioran and especially Ray Brassier, with his devastating book Nihil Unbound. Just being against life does not mean that these ideas are untrue or can be excluded from the realm of philosophical thought. When we take philosophical thought seriously, we cannot reject conclusions just because they do not fit our restricted human-centric point of view. That is what I mean by saying the interests of life are not necessarily those of philosophy.

In the context of the relation between psychosis and philosophy, this is important to consider, and this also sweeps away all romantic humanist notions of both philosophy and psychosis. Consider the case of someone like Anders Breivik, the Norwegian terrorist and right-wing extremist. Some philosophies or world views, as well as some particular forms of madness, are thoroughly destructive and devoid of good intentions. They are closer to the darker variety of the mystical aspect of madness. American philosopher William James described it as diabolical mysticism.

In such cases, the philosophical aspect of the psyche would not only consist of the strange ineffable character of an experience filled with awe and puzzlement, but also of an intra- and interpersonal struggle between life-affirming forces and life-denying, a-human or antihuman forces. The implicated question is whether we must eradicate such poisonous ideas, or must we taste and experience them ourselves, to examine the enemy, and immunize ourselves against them, with all kinds of risk of contamination? The implicated practical problem for psychiatrists is to make responsible decisions in matters that comprise philosophical and theological as well as political complexities. What is demanded of the psychiatrist here has hardly anything to do with scientific knowledge; it is also difficult to be captured in ethical guidelines, and it can only be referred to with notions like prudence.

AFTAB: You have warned against romanticization of psychosis. From what I can tell, while you seem to be in favor of controlled explorations of psychosis by means of philosophy or mysticism, you do not seem to wish the clinical, raw experience of psychosis upon anyone. While you have derived insights from your experience of psychosis, I imagine that you are also glad to have come out of psychosis. How do you think we can reconcile the tension, to the extent that it exists, between the clinical and philosophical attitudes toward psychosis? Individuals with psychosis are often tremendously distressed and impaired, and they typically require some form of clinical care to help navigate this distress and impairment. How do we reconcile this with the romantic image of the madman as a misunderstood mystic or an unrecognized philosopher or with the more prosaic image of a deviant whose deviance has been pathologized?

KUSTERS: I think that the clinical attitude should incorporate the philosophical attitude, and clinicians should be educated in this. In fact [he laughed], I would recommend that they should all read my book, or perhaps follow the course I teach about my book! In my book, they would indeed meet these images of the misunderstood mystic, the unrecognized philosopher, and the pathologized deviant. However, my book does not want them to accept these images as the essence of psychosis, but as starting points from which a dance, dialectic, or conversation may begin between philosophy and madness, the rational and the irrational, without being condemned to one position or the other.

AFTAB: Thank you!

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

Dr Aftab is a psychiatrist in Cleveland, Ohio, and a clinical assistant professor of psychiatry at Case Western Reserve University. He is a member of the executive council of the Association for the Advancement of Philosophy and Psychiatry and has been actively involved in initiatives to educate psychiatrists and trainees on the intersection of philosophy and psychiatry. He is also a member of the Psychiatric Times™ Advisory Board. He can be reached at awaisaftab@gmail.com or on Twitter @awaisaftab.

Dr Aftab has no relevant financial disclosures or conflicts of interest. Dr Kusters receives royalties from the sales of his book and generates income from the online course he offers on his website.

REFERENCE
chizophrenia is a chronic, serious and often severely disabling brain disorder that affects more than 20 million people worldwide. The condition is characterized by positive symptoms, such as hallucinations, delusions and disorganized thinking as well as negative symptoms, including lack of emotion, social withdrawal, lack of spontaneity and cognitive impairment which can include problems with memory, attention, and the ability to plan, organize and make decisions. Symptoms typically present in the early to mid-20s, and evidence suggests that treating schizophrenia within the first three years of illness with pharmaceutical, social and psychological interventions can improve outcomes.

Despite schizophrenia ranking as one of the top 15 leading causes of disability globally, medications to treat it have worked largely the same way since the 1950s. Antipsychotics are the most commonly-prescribed medicines for schizophrenia, belonging to one of two types – typical or atypical. Typical antipsychotic drugs, first introduced in the 1950s, are strong dopamine D2 receptor antagonists and therefore are often associated with risk for hyperprolactinemia and extrapyramidal symptoms (EPS) such as tremors, muscle contractions, and other involuntary muscle movements that may be debilitating.

After many years of research, atypical antipsychotics were developed to address some of the challenges of the typical antipsychotics and were introduced to patient care in the early 1990s. Atypical antipsychotics are also antagonists for the dopamine D2 receptor but with a lower affinity, and added antagonism at serotonin 5-HT2a receptors. Though these medications have a lower risk of hyperprolactinemia and EPS than their predecessors, atypical antipsychotics are often associated with an increased risk for cardiometabolic symptoms including weight gain and diabetes. Additionally, while atypical antipsychotics may effectively treat psychosis and other positive symptoms of schizophrenia, they are less effective at treating negative and cognitive symptoms. As these symptoms can have an impact on quality of life for patients and care partners, this remains an important area of unmet need in the management of schizophrenia.

Discovering New Targets – the Potential of TAAR1 Agonism

Although there has been significant interest over the last 60 years to develop novel treatments for schizophrenia that do not block dopamine D receptors, most of these efforts have been unsuccessful in the clinic. However, researchers have recently identified a new promising therapeutic target for the treatment of schizophrenia: trace amine-associated receptor 1 (TAAR1). TAAR1 is a member of a family of G-protein coupled receptors called TAARs, which are activated by trace amines. Trace amines are structurally related to classical neurotransmitters such as dopamine and serotonin, but are present in much lower concentrations in the body. TAAR1 is widely expressed throughout the brain and has been found in areas that are associated with the emergence of schizophrenia symptoms, including the ventral tegmental area (VTA) and dorsal raphe nucleus (DRN), which produce dopamine and serotonin, respectively.

“We are just beginning to understand the full range of activity of TAAR1 and how we can leverage this knowledge to advance treatment for patients with a variety of neuropsychiatric conditions,” said Andrew J. Cutler, M.D., Clinical Associate Professor of Psychiatry at SUNY Upstate Medical University. “Early research on the role of TAAR1 in the brain is promising, and we are hopeful that a better understanding of TAAR1 may make a real difference in mitigating the array of symptoms of schizophrenia and other brain disorders.”

Understanding the potential of TAAR1 agonism has unlocked new avenues that aim to treat schizophrenia in a new way. Preclinical evidence shows TAAR1 modulates the signaling of several neurotransmitter systems (including dopamine, serotonin, and glutamate) which are often dysregulated in schizophrenia.

Preclinical data demonstrate that TAAR1 agonism produces antipsychotic-like effects without D2 or 5-HT2a receptor antagonism. Studies have found that TAAR1 agonists can reduce the firing of dopaminergic and serotonergic neurons and can also increase transmission through glutamatergic neurons – three concepts important to the treatment of schizophrenia symptoms.

A Novel Compound Targeting TAAR1

Ulotaront (SEP-363856) is a TAAR1 agonist with serotonin 1A (5-HT1A) activity.
agonist activity and is the first TAAR1 agonist to enter Phase 3 clinical studies to evaluate the treatment of adults and adolescents (ages 13-17) with schizophrenia. The stem –taront, connotes ulotaront as a member of the TAAR1 agonist class, differentiating itself from suffixes used to denote other pharmacologic substances used among approved antipsychotics (e.g., -done, -pine, -pip).

Results published in The New England Journal of Medicine of the 4-week, double-blind, placebo-controlled pivotal study (SEP361-201) and the 26-week open-label extension study (SEP361-202) showed that treatment with ulotaront significantly reduced both positive and negative symptoms of schizophrenia. The pivotal study met its primary endpoint of change in Positive and Negative Syndrome Scale (PANSS) total score at Week 4, with a statistically significant and clinically meaningful improvement of -17.2 points (ulotaront) vs -9.7 (placebo) points from baseline (p=0.001). Ulotaront demonstrated a safety and tolerability profile comparable to placebo. The most common adverse events associated with ulotaront were somnolence, agitation, nausea, diarrhea, and dyspepsia. There were no clinically meaningful changes observed on metabolic parameters (including weight, lipids and glucose) or prolactin levels in either study. Additionally, there were no significant differences observed in potential movement disorders between ulotaront and placebo patients.

“Overall, findings from the ulotaront pivotal 4-week trial and 26-week open-label extension suggests that TAAR1 agonism may treat positive and negative symptoms of schizophrenia without significantly increasing weight, elevating prolactin or glucose, or inducing movement disorder adverse effects,” said Dr. Cutler. “The results of the study are promising and demonstrate the potential of ulotaront in the treatment of schizophrenia.”

Ulotaront is currently being evaluated in the global Phase 3 DIAMOND clinical trial program, which includes four studies designed to evaluate the safety, efficacy, and tolerability of ulotaront for the treatment of people with schizophrenia.

To learn more about TAAR1, visit: www.sunovion.com/taar1modvideo

To watch a video explaining TAAR1's ability to regulate neurotransmitter systems important to mood, psychosis, reward-processing and cognition, researchers believe TAAR1 agonists have potential as a therapeutic target for several neuropsychiatric disorders, including schizophrenia.

Based on TAAR1’s ability to regulate neurotransmitter systems important to mood, psychosis, reward-processing and cognition, researchers believe TAAR1 agonists have potential as a therapeutic target for several neuropsychiatric disorders, including schizophrenia.

**References**

13. Sotnikova TD, Caron MG, Gainetdinov RR. Trace amine-associated receptors as emerging therapeutic targets. Mol Pharmacology. 2009;76(2):229-235
Mr Morris is diagnosed with delirium. According to the DSM-5, delirium is “a disturbance in attention and awareness” with an additional cognitive disturbance (e.g., memory deficit, disorientation, language, visuospatial ability or perception) that develops over “hours to a few days,” “represents a change from baseline,” and “fluctuates in severity during the course of a day.” Furthermore, it is due to 1 or multiple underlying medical etiologies and is not better explained by another psychiatric diagnosis.1

There are 3 subtypes of delirium: hyperactive, hypoactive, and mixed. In our vignette, the acute agitation and interference with medical treatment quickly brings this patient to staff attention. However, the literature shows that delirium is missed in 57% to 83% of emergency department (ED) assessments, and in admitted patients, more than 90% of cases will be missed if it is not diagnosed in the ED.2 According to a prospective study in The University of Texas MD Anderson Cancer Center Emergency Medicine department, patients with cancer who presented with delirium are more likely to be admitted to the hospital, require an ICU admission, and have worse outcomes.3 In patients with advanced cancer, 16% of the consultations were for delirium, yet delirium was diagnosed by the palliative care team in 56% of the patients.4 In patients with advanced cancer, delirium is associated with a poor prognosis, increased hospital length of stay, and increased hospital costs.5

CASE STUDY
“Mr Morris,” aged 70, had melanoma and, following treatment, is in remission. Mr Morris presents to your outpatient psychiatry clinic for an initial evaluation. He has never had medical issues otherwise and has never been diagnosed with a mental illness until a hospital stay about 6 months ago. His family provided collateral information. They were very concerned because, while he was hospitalized, he was “talking nonsense” and accusing his wife of 50 years of having an extramarital affair. He was also pacing and saying random things about memories which they thought were made up, such as the example above. Inquiring about this in your clinical assessment, the patient says, with some bashfulness, “Well, you know, we met at 15 and a lot of people liked her. I was the lucky one.” But he does not recall anything he said while hospitalized. He was discharged on haloperidol, but the family stopped it after reading about the black box warning for antipsychotics in older adults. A careful history taking is negative for psychotic symptoms including hallucinations, delusions, and disorganization, and for negative symptoms of psychosis. Since being home and off medications, he is back to his usual self.

You ask for medical records and find out that the medication was started after an episode during which the psychiatry consult and liaison service consulted for overnight confusion and agitation. Mr Morris had started to pull out his IV lines and catheter, then tried to undress and walk down the hallway, but was falling down, given physical weakness. The medication was not stopped upon symptom resolution and patient discharge.

Discussion
Mr Morris is diagnosed with delirium. According to the DSM-5, delirium is “a disturbance in attention and awareness” with an additional cognitive disturbance (e.g., memory deficit, disorientation, language, visuospatial ability or perception) that develops over “hours to a few days,” “represents a change from baseline,” and “fluctuates in severity during the course of a day.” Furthermore, it is due to 1 or multiple underlying medical etiologies and is not better explained by another psychiatric diagnosis.1

There are 3 subtypes of delirium: hyperactive, hypoactive, and mixed. In our vignette, the acute agitation and interference with medical treatment quickly brings this patient to staff attention. However, the literature shows that delirium is missed in 57% to 83% of emergency department (ED) assessments, and in admitted patients, more than 90% of cases will be missed if it is not diagnosed in the ED.2 According to a prospective study in The University of Texas MD Anderson Cancer Center Emergency Medicine department, patients with cancer who presented with delirium are more likely to be admitted to the hospital, require an ICU admission, and have worse outcomes.3 In a retrospective chart review of 61 consecutive inpatient palliative care consultations in patients with cancer, 56% of the patients were for delirium, yet delirium was diagnosed by the palliative care team in 56% of the patients.4 In patients with advanced cancer, delirium is associated with a poor prognosis, increased hospital length of stay, and increased hospital costs.5

In patients with advanced cancer, delirium is associated with a poor prognosis, increased hospital length of stay, and increased hospital costs.5

In this installment of Tales From the Clinic: The Art of Psychiatry, we discuss delirium, an underrecognized, underdiagnosed medical condition. Elderly patients, who experience more delirium than their younger counterparts, often receive a misdiagnosis. They may be mistakenly labeled as having a mental illness and given psychotropic medications that have an elevated adverse effect burden.
cancer, terminal delirium prevalence rates approach 90% in end-of-life care. Delirium can be related to cancer, its treatment (ie, radiation, chemotherapy), and noncancer-related pathology. In delirium, there are unmodifiable factors that predispose a patient to developing the condition and there are precipitating factors that can be clinically addressed. Common predisposing factors that increase the risk of developing delirium include older age, a neurocognitive disorder, visual and hearing impairments, and chronic organ dysfunction. Precipitating factors to consider include psychoactive medications (including opioids and corticosteroids), infections, hypoxia, withdrawal, metabolic derangement, dehydration, and acute infections, especially pneumonia and urinary tract infections.

To improve the delirium, the precipitating cause or causes should be treated. Lawlor studied delirium in patients with advanced cancer and determined that reversibility was most common when addressing the precipitating factors of psychoactive medications, specifically opioids, and dehydration. The pathophysiology of delirium is complex, and there are hypotheses to explain the role of inflammation, oxidative stress, and neurotransmitters in the condition. Delirium is a state of low acetylcholine and high dopamine, which is important to consider when reviewing if a medication could be contributing to a patient’s delirium.

Psychoactive medications include opioids, benzodiazepines, antidepressants, antihistamines, and anticholinergics. When delirium develops, it is important to consider these medications as potential precipitating factors. Anticholinergics and antihistamines commonly worsen delirium and should be discontinued. The duration of use and dose of benzodiazepines should be closely examined in delirium because the sudden cessation of a medication on which a patient is dependent could produce a withdrawal delirium; however, ongoing use in a patient without tolerance could result in intoxication.

Opioid medications are frequently used for cancer-related pain. However, opioid toxicity can occur, especially with rapid dose escalation for pain control. Medication adjustments including opioid rotation are helpful in managing opioid toxicity and managing pain when side effects limit further titration. Opioid rotation is the practice of transitioning to a different opioid with the goal of optimizing the balance of pain control to side effects. The clinical practice guidelines for the European Society for Medical Oncology recommend opioid rotation, which can allow for dose reduction given opioid equianalgesic dosing.

Corticosteroids are more likely to have psychiatric sequelae at higher doses. Findings from 1 study revealed that the rate of psychiatric reactions is 1.3%, 4.6%, and 18.4% at doses of prednisone less than 40 mg/day, 41 to 80 mg/day, and greater than 80 mg/day, respectively. Mania, psychosis, and delirium can develop in the acute course of corticosteroid use. Depression, which is part of the differential diagnosis for hypoactive delirium, is more likely to develop with chronic steroid use. Although corticosteroids can contribute to delirium, they can also improve cognition by decreasing edema secondary to primary or metastatic brain tumors. It is important to consider the timeline of symptom development and treatment when considering the impact of corticosteroids in delirium. Delirium secondary to corticosteroid exposure is likely to occur within 1 to 2 weeks and at a higher incidence for higher doses. Furthermore, delirium caused by corticosteroids has been associated with delirium-related distress. As clinically indicated, minimizing the dose and duration of treatment can improve delirium related to steroid administration.

Delirium is treated by correcting the precipitating factors; however, nonpharmacologic and pharmacologic strategies are used to assist in its management. Nonpharmacologic management includes frequent reorientation, patient access to glasses and hearing aids, familiar surroundings (consistent care team, family present or their pictures available), regulating sleep/wake cycles (lights on and blinds open the during the day, but lights off and blinds closed at nighttime), clustering care to daytime hours, minimizing lines including IVs and urinary catheters, and encouraging patient mobilization. Regarding pharmacologic management, a 2018 Cochrane review of antipsychotic treatment in non-ICU patients concluded that the current evidence to recommend for or against the use of antipsychotics is of low quality, as antipsychotic use had no statistically significant impact on delirium resolution or severity. In clinical practice, pharmacologic management with antipsychotics is primarily used to target distressing agitation, hallucinations, and delusions. In refractory agitated delirium, the involvement of palliative care and palliative sedation can also be considered. During the investigation into the etiology and treatment of delirium in a patient, it is important to consider the goals of care. When goals of care are addressed early, a patient’s wishes are known to the team and the substitute decision maker if a patient’s mentation becomes altered. Established goals of care at the end of life allow palliation while limiting more aggressive interventions if it is the patient’s desire. Aggressive interventions at end of life have been associated with worse patient quality of life and worse bereavement in their caregivers.

Concluding Thoughts
It is always important to remember to consider the system you are treating, which is more than the patient. Breitbart et al showed that 53.5% of peracute delirium, brain metastases, and KPS scores below 30, which indicate “severe physical debilitation and near death.” Nursing staff are more likely to be distressed when a delirious patient has more severe delirium and hallucinations. While treating the delirium, consider the potential traumatic impact upon the patient, family, and staff, and offer ongoing support.

Dr Howse is a psychiatrist at Baylor College of Medicine in Houston, Texas, and a psychosomatic medicine specialist.

REFERENCES
Things You Should Know About Recent Trends in Treating Psychiatric Disorders

The treatment landscape for psychiatric disorders is constantly changing due to emerging data, and the 2021 Annual Psychiatric Times® World CME Conference™ provided updates from expert faculty in the field. Here are 3 things you should know about developments in the management of major depression, bipolar disorder (BD), and schizophrenia.

1. Treatment-resistant depression continues to be an obstacle for patients and clinicians.

Major depression is one of the most common mental disorders in the United States, affecting approximately 8% of adults older than 20 years of age. Treatment aims to reduce symptoms and improve quality of life, but treatment-resistant depression (TRD) is a common problem. Frequently, patients require multiple therapies to reach remission, but no widely accepted definition of TRD exists.1-3

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study was a series of randomized controlled trials (RCTs) starting with citalopram as initial therapy for depression and progressing up to 4 treatment steps with various classes of antidepressants if needed.4 Patients advanced to the next treatment step if they were unable to achieve remission or tolerate the medication. These studies found a decline in remission rates as the number of prior treatment failures increased.

The relationship between prior treatment failure and remission rates in major depression is shown below.5,6 Genetic testing and therapeutic drug monitoring (TDM) are sometimes employed to optimize antidepressant therapy. Genetic testing can be used to assess genes that may affect the pharmacodynamics and pharmacokinetics of antidepressants.7 The efficacy of these tests in establishing optimal treatment is still being determined.

TDM may be useful to evaluate a patient's drug concentration levels and dosing, as well as to determine adherence. When interpreting TDM, important points to consider include the dose the patient should be taking, whether the patient has reached steady state, and timing of the last dose in relation to when the sample is taken.8 The relationship between prior treatment failures and remission rate in major depression is shown in Table 1.

Table 1. Relationship Between Prior Treatment Failures and Remission Rate

<table>
<thead>
<tr>
<th>Number of prior treatment failures</th>
<th>Remission rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>No or limited prior treatment</td>
<td>27.5%</td>
</tr>
<tr>
<td>1 prior failure</td>
<td>21.2%</td>
</tr>
<tr>
<td>2 prior failures</td>
<td>16.2%</td>
</tr>
<tr>
<td>3 prior failures</td>
<td>6.9%</td>
</tr>
</tbody>
</table>

In accordance with ACCME Guidelines, PER® has identified and resolved all COI for faculty, staff and planners prior to the start of this activity by using a multistep process.

To learn more about this topic, including information on the 2021 Annual Psychiatric Times™ World CME Conference™ go to gotoper.com/go/psych2021activity

Instructions for Participation/How to Receive Credit

Read this activity in its entirety.

Go to gotoper.com/go/psych2021enduring to access and complete the post-test.

Answer the evaluation questions.

Request credit using the drop-down menu. You may immediately download your certificate.
Second-generation antipsychotic use is rising in patients with BD.

BD affects approximately 4.4% of people in the United States. Lithium was a previous standard of care in BD due to its efficacy in suicide prevention. However, lithium is associated with adverse effects and requires intense monitoring.

In outpatient BPD visits, SGA use increased from 12.4% to 51.4%.

Treatment options for BD have increased in the last 2 decades, as several second-generation antipsychotics (SGAs) have indications for BD management, including aripiprazole, asenapine, cariprazine, laruxadone, olanzapine, quetiapine, risperidone, and ziprasidone. Data from the National Ambulatory Medical Care Survey show an increase in the use of SGAs in outpatient psychiatrist visits for BD from 12.4% in 1997-2000 to 51.4% in 2013-2016. During the same time periods, mood stabilizer use decreased from 26.4% to 26.3%. Although the use of SGAs has largely replaced mood stabilizers, comparative efficacy data are lacking. Lithium is still a treatment of choice based on a systematic review of guidelines.

An increase in the use of antidepressants without a mood stabilizer was also noted, rising from 17.9% in 1997-2000 to 40.9% in 2013-2016. Although patients with BD spend much more time depressed than manic, the use of unopposed antidepressants is controversial. Antidepressants may trigger a switch to mania or hypomania or induce rapid cycling, and their efficacy in treating BD has not been validated.

This increase occurred even though antidepressants are less recommended in treatment algorithms and should be used in combination with a mood stabilizer or antipsychotic.

An increase in the use of antidepressants was noted from 17.9% in 1997-2000 to 40.9% in 2013-2016. Although patients with BD spend much more time depressed than manic, the use of unopposed antidepressants is controversial. Antidepressants may trigger a switch to mania or hypomania or induce rapid cycling, and their efficacy in treating BD has not been validated.

This increase occurred even though antidepressants are less recommended in treatment algorithms and should be used in combination with a mood stabilizer or antipsychotic.

Lithium is still a treatment of choice based on a systematic review of guidelines. An increase in the use of antidepressants without a mood stabilizer was also noted, rising from 17.9% in 1997-2000 to 40.9% in 2013-2016. Although patients with BD spend much more time depressed than manic, the use of unopposed antidepressants is controversial. Antidepressants may trigger a switch to mania or hypomania or induce rapid cycling, and their efficacy in treating BD has not been validated.

This increase occurred even though antidepressants are less recommended in treatment algorithms and should be used in combination with a mood stabilizer or antipsychotic.

Long-acting injectables reduce hospital readmissions in patients with schizophrenia.

Adherence is a common concern in the management of schizophrenia, with 74% of patients discontinuing treatment within 18 months. A combination of factors—including cognitive impairment, adverse effects, and dosing frequency—attribute to nonadherence, and nonadherence is associated with increased risk of relapse and hospitalization.

Long-acting injectables (LAIs) administered every 2 to 4 weeks are recommended by clinical guidelines to address adherence barriers seen with oral antipsychotics. However, LAIs are underused. Patient fear of injections and prescriber fear of adverse effects without the possibility of rapid discontinuation are reasons cited for LAI underuse.

Previous RCTs have called into question the advantages of LAIs compared with oral antipsychotics. However, patients who are nonadherent are often excluded from trials; similarly, patients in the trials may be more motivated to be adherent.

A 10-year retrospective study of claims databases sought to determine the effectiveness of LAIs in real-world settings. It included 75,274 patients hospitalized with schizophrenia and found that LAIs decreased readmission rates by 29% compared with oral treatment. In patients with repeated admissions, LAIs reduced the readmission rate by 58%.

CME POSTTEST QUESTIONS

1. Which of the following statements is true regarding treatment failure for major depressive disorder?
   A. There is no relationship between prior treatment failures and remission rates for current treatment.
   B. Remission rates for current treatment drop predictably with an increasing number of prior treatment failures.
   C. Patients who are historically more resistant to treatment have a longer time before relapse compared to those with less resistance to prior treatment.

2. Which of the following statements best describes a trend in pharmacological treatment of bipolar disorder in the outpatient setting from 1997 to 2016?
   A. Antipsychotic use increased significantly.
   B. Antidepressant use decreased significantly.
   C. Use of mood stabilizers remained unchanged.

3. In a recent study of more than 75,000 patients hospitalized with schizophrenia, the use of long-acting injectable antipsychotics reduced the readmission rate by how much compared to patients on oral medication in real-world settings?
   A. 10%
   B. 19%
   C. 29%
   D. 79%

To learn more about this topic, including information on the 2021 Annual Psychiatric Times World CME Conference go to gotoper.com/go/psych2021activity
Doorknob Moments
Why They Happen and How to Use Them

Daniela V. Gitlin, MD

We have all had the experience of a patient dropping a bomb—a critical disclosure that moves the treatment forward—on their way out, with a hand on the doorknob.

When the patient becomes distraught following a shocking revelation, it feels at least unkind and at worst harmful to say, “Sorry, too bad you’re bleeding, but we don’t have time to pack that wound.” What to do?

During my residency, I was taught that ending on time is therapeutic for the patient, but not why. Reviewing the literature for guidance on how to better manage this phenomenon, I found only content-driven hypotheses: the patient’s psychodynamics and pathology; the therapeutic relationship; the meaning of time vis-à-vis development and childhood events; the economic value of the time and duration of session time on outcomes; and others.

None had sufficient power to quell the doubt that I might violate the do-no-harm mandate if I insisted we end on time.

The Power of the Deadline
Running late derails the day’s schedule (stressful for me) and inconveniences subsequent patients (stressful for them, and possibly undermining their treatments). I know a bomb will drop, but not when, how, or who will drop it. When it hits, making a judgment call about whether to run over or not has been an on-going source of professional stress. Complaining about this to other professionals in my life (an accountant, business consultant, family practice doctor, broker, lawyer, among others) I discovered—surprise—their clients drop bombs on them too.

If the phenomenon is independent of content, then it is likely that the structural element—the impending end of the session—must cause the disclosure.

No deadline, no revelation. Artists use this when producing new work. As Duke Ellington said, “I don’t need time. I need a deadline.”

Left-Brain Physicians, Right-Brain Patients
Conceptualizing the functional differences between patient and clinician in the treatment relationship as a metaphor for the functional differences between right and left cerebral hemispheres has surprisingly useful clinical ramifications.

At the cellular level, the brain is a vast, mind-bogglingly complex network of connectivity and plasticity that defies our wish to tag specific areas with specific functions. On the macro level though, findings from split brain studies of individuals whose right and left cerebral hemispheres have been surgically separated to treat intractable seizures suggest that each hemisphere, independent of the other, can do all an individual needs to live in the world (with the exception of speech, which is a function of the left side only). There is one caveat: it appears that the 2 sides differ profoundly in mode of functioning, strengths and limitations, and worldview.

The right side’s focus is broad. Widely networked throughout both hemispheres, it uses bodily sensation (visual, auditory, touch, taste, smell) to process experience, and thinks in images. It lives concretely, moment by moment, in the present. It is comfortable with uncertainty and the unknown because it interfaces directly with the external environment (ie, new data).

The right side processes time without a break in continuity, as an ongoing narrative. It is generative and creates narrative structures to present to the outside world—stories, drawings, dances, songs—without being formally taught how to make them. Somehow, it knows what to do, and does it without conscious intent. Classic examples include the way children draw without a plan, and your hand pulls back from a hot burner before you realize it is burned.

The left side is heavily interconnected within itself, less so globally. This facilitates its primary strength—narrow focus—but it also reflects on a neural level the self-referring nature of its operations. It deals only with what it already knows (ie, the past, and the world it has made for itself). It is analytic, critical, and logical. It uses language to bring to consciousness sensory input delivered by the right side. However, that takes time. The right side has already non-verbally instructed your
The impending end of the session—the deadline—somehow empowers the patient’s right hemisphere to disclose new data against the left’s nay-saying.

Artists who regularly birth new work know newborn drafts should not be evaluated, judged, and criticized immediately after delivery. Such feedback by the verbal self (left brain) is almost always negative, because it rejects what is new in favor of what it already knows. After a patient drops a bomb, we too need the session to end to prevent ourselves from sharing unthought-through reactions.

Before this formulation came to me, the patient’s distress following a last-minute disclosure would influence when I ended the session. Now I end the session on time because it is the therapeutic thing to do.

I predict for patients that they will, at some point, find themselves upset by something they revealed at session’s end. When that happens, they are reassured to be reminded that it is part of the process.

Accepting this premise eliminates the need to make a judgment call under time pressure. But it is still a challenge to end the session gracefully while taking into account the patient and the situation at hand.

Case Studies

The Covest. My patient “Kate,” while putting on her coat, says she has taken a month’s worth of lithium 2 hours before the session, after a fight with her boyfriend. It goes without saying, but I will say it anyway: the content of this article does not apply to a medical emergency. That requires crisis intervention. I called 911 and rescheduled my next patients in order to get Kate admitted.

Dr Gitlin is a rural psychiatrist in private practice in upstate New York. Her first book Practice, Practice, Practice: This Psychiatrist’s Life was selected as a Finalist by the 2021 International Book Awards in the Health: Psychology and Mental Health category. Her website is danielagitlin.com.

REFERENCES

Mood Disorders

BIPOLAR UPDATE

Mania With Psychosis vs Schizophrenia vs Schizoaffective Disorder, Bipolar Type

David N. Osser, MD

(This is the third part of the How To Diagnose Bipolar Disorder series—Ed.)

Have you had difficulty with differential diagnosis when the patient has manic symptoms and psychosis? In 2013, the DSM-5 made the issue clearer with significant changes in the criteria defining the quantity and nature of mood symptoms in these diagnoses. As a result, more patients will be diagnosed with schizoaffective compared with when using DSM-IV in either the TM or later “Text Revised” TR version. I will propose some of the implications for psychopharmacology.

In the schizophrenia D criteria in DSM-5, the patient should have no mood episodes (ie, meeting full criteria for mania or depression) during the active phase of the illness, or, if the patient has episodes, those episodes occur during a minority (ie, up to 50%) of the total duration of the illness (active and residual phases). In other words, a patient with schizophrenia can have a full manic syndrome present for up to 50% of the time, as long as the other schizophrenia criteria are met. Those criteria include, from the A criteria, positive symptoms during the acute phase; the B criteria of illness duration of at least 6 months of the active and residual phases; the C criteria of deterioration in functioning compared to premorbid levels; and the E criteria of no explanation of it from a substance or medical illness.

In the DSM-IV D criteria for schizophrenia, the requirement was that any mood episodes had to be brief in duration compared with the duration of the illness. An example of “brief” was a 5-week period of mania or depression in a patient who was ill for 4 years, which would translate to having a mood syndrome present 2.5% of the time. So, with DSM-IV, individuals with schizophrenia could not experience much time with any mood syndrome to meet the schizophrenia criteria. Also, study results found that patients diagnosed using the criteria very often evolved over time to having a schizophrenia diagnosis, whereas schizophrenia diagnoses under DSM-IV tended to be stable over time.

Notably, study results have shown that when the DSM-IV criteria for schizoaffective disorder were in use (1994-2013), clinicians did not seem to use it for diagnoses. They overdiagnosed it using unspecified criteria. Also, study results found that patients diagnosed using the criteria very often evolved over time to having a schizophrenia diagnosis, whereas schizoaffective diagnoses under DSM-IV tended to be stable over time. Accordingly, with the new, more inclusive DSM-5 criteria for schizophrenia, the diagnosis should continue to be stable.

How about the diagnosis of mania with psychosis? In psychotic mania (in DSM-IV and DSM-5), the psychosis appears only during the time the patient is meeting criteria for mania, not after it as in schizoaffective disorder. Usually, the psychosis develops during the most severe part of the mania and tends to resolve early as the episode improves, and before the rest of the manic symptoms resolve.

Now that you have an accurate diagnosis per DSM-5, what is the psychopharmacology treatment? If the diagnosis turns out to be schizoaffective disorder, there is no demonstrated value to adding non-antipsychotic mood stabilizers (like lithium or valproate) to the antipsychotic for the manic component, according to the evidence reviewed in the Schizophrenia Patient Outcomes Research Team (PORT) guidelines. These additions only potentially contribute adverse effects. The usual psychopharmacology algorithm of employing 2 adequate monotherapy trials of antipsychotics followed by consideration of clozapine probably still applies for DSM-5 schizophrenia. If the diagnosis is bipolar with psychosis, you can use those traditional mood stabilizers as well as antipsychotics. Study results show that psychotic mania responds just as well to either class of drugs.

But what if the patient meets the DSM-5 criteria for schizoaffective disorder, bipolar type? We do not know how to treat it, just as we did not know how to treat DSM-IV schizoaffective disorder, bipolar type.

There are almost no studies, no algorithms to consult, no FDA-approved options (although some paliperidone products did manage to get the only FDA approval for schizoaffective disorder). There is still serious doubt that the condition even exists as a valid entity, and it is likely that the current criteria capture only some patients who belong in either the schizophrenia spectrum or the bipolar spectrum.

It is suggested that you treat with your best psychopharmacology algorithm for schizophrenia or for bipolar with psychosis, depending on which diagnostic category best represents the patient’s presentation. If the results are unsatisfactory, try switching to your algorithm for the other diagnosis. This may produce better results than improvising with pure guesswork.

Dr. Osser is co-director of the VA National Bipolar Disorder Telehealth Program and an associate professor of psychiatry at Harvard Medical School at the VA Boston Healthcare System.

REFERENCES

Chatbots for Child Mental Health Care: Helpful, but Limited

Artem Trotsyuk, MS; and Jack Turban, MD, MHS

Childhood: a carefree time for many. However, children today face countless sources of stress: academic pressure, schedules crammed with activities, lack of sleep, bullying, family instability, world events, social media, and more. Mental health issues among children are growing at a dangerous rate, and it is important that we use all of our innovative technologies to help them. It is clear that far too many children are having trouble coping with the stresses of daily life. An estimated 7.7 million children have at least 1 mental health disorder, and half are not receiving the treatment they need. More broadly, an estimated 15 million children in the United States alone are in need of a psychiatrist. More than 4 million children and teenagers have been diagnosed with anxiety, and nearly 2 million have been diagnosed with depression, according to a study published in The Journal of Pediatrics. This is resulting in far too many tragic outcomes. A study published in The New England Journal of Medicine reported that a fifth of deaths among children and adolescents in 2016 were suicides.

Yet with such a high demand for doctors, there are only approximately 8,000 practicing child psychiatrists in this country.” At a time when health care professionals are stretched thin, access to child psychiatry is at an all-time low, and the inequities of our health care system have been made clearer than ever. Can artificial intelligence (AI) help alleviate some of these problems?

Chatbots: Effective Therapy?

AI, more broadly, is already “transforming the world,” and has found uses reading CT scan images, powering autonomous vehicles, assisting with national defense, and more. It is a powerful technology that will continue to be used in more areas, but how can it be applied to children’s mental health? Enter AI chatbots—programs designed to carry on realistic text- or voice-based conversations with patients and offer advice. They can be available to talk 24/7 and could be infinitely scalable, providing help to millions more people.

They are already helping in many situations. More than 40 different kinds of mental health chatbots exist, mostly focused on treating depression or anxiety. And they work: According to findings from a 2017 study by investigators from Stanford University School of Medicine and the developers of the aptly named “Woebot,” the bot was effective in reducing depression and seen as empathetic among college students after just 2 weeks of therapy modeled after cognitive behavioral therapy, a well-known method employed by many human therapists. The study authors wrote:

“The number of participants reporting that the bot felt empathetic is noteworthy, and comments that referred to the bot as ‘he,’ ‘a friend,’ and a ‘fun little dude’ suggest that the perceived source of empathy was Woebot rather than the bot’s developers.”

In another study, Australian teenagers were tasked with helping develop a mental health chatbot, providing input on its gender and the type of slang it should use. (They chose a gender-neutral bot named Ash that was familiar with “brekky” for breakfast and “footy” for football.) The teenagers in that study said they were not always able to get help from existing school resources, and the investigators hoped the chatbot would be able to fill some of those gaps.

Chatbots have the potential to be a powerful tool to help millions—likely even more than the number of individuals diagnosed with anxiety or depression. As many individuals struggle with their mental well-being without a formal diagnosis of a mental health disorder, perhaps mental health chatbots could also help reduce the stigma associated with asking for help. But chatbots cannot be the only way we provide help to the most vulnerable among us. AI tools must be part of a holistic approach led by qualified and experienced doctors. Just as medicine is not the only tool doctors use to treat illness or injury, chatbots must not be the only way we improve the mental health of children.

“Good mental health and well-being is about more than just a lack of illness,” the authors of the Australian study wrote. “Focusing on positive coping and building resilience is important in establishing a holistic approach to health, addressing both physical and psychological experiences of youth. It is clear that young people being aware of mental health and well-being literacy has implications for the promotion of healthy well-being and early prevention of mental health disorders.”

Concluding Thoughts

We are facing a serious mental health crisis among young individuals, and we must use every tool at our disposal to help. AI is not replacing doctors—rather, it is a tool that allows for the democratization of care and increased access to combat non-complex mental health issues. Doctors will remain a valuable asset for treating more complex disorders. However, chatbots are a powerful tool that should be adopted more widely because anything that can be used to improve the well-being of children must be considered.

Mr Trotsyuk is a graduate fellow in bioengineering and computer science at Stanford University School of Medicine. Dr Turban is chief fellow in child and adolescent psychiatry at Stanford University School of Medicine.

REFERENCES
Advances in Treatments for ADHD

**Laurence Greenhill, MD**

Treatments recently approved by the US Food and Drug Administration (FDA) for pediatric patients with attention-deficit/hyperactivity disorder (ADHD) include 2 medications that address some of the common issues associated with standard stimulant treatments. Another development is use of devices to manage ADHD symptoms (Table).

### Delayed-Release Stimulant

Methylphenidate hydrochloride (Jornay PM), a delayed-release/extended-release methylphenidate, was approved by the FDA in 2018 and became commercially available in 2019. It differs from the other methylphenidate-based stimulants in that it is administered before bedtime—between 6:30 PM and 9:30 PM—to take effect in the morning when the child rises.

This delayed action addresses a common problem many families face when stimulants are administered upon rising: Patients are focused and ready to work by the time school starts, but getting children to school is a struggle, which adds burden on caregivers. Results from a randomized controlled trial published in April 2021 found that this formulation does indeed help in that respect. Investigators found a marked decrease in burden on caregivers. Results from a randomized controlled trial published in April 2021 found that this formulation does indeed help in that respect. Investigators found a marked decrease in burden on caregivers.

### Nonstimulant Medication

In April 2021, the FDA approved vilotrazine (Qelbree) for treatment of ADHD in patients aged 6 to 7 years. Like atomoxetine hydrochloride (Strattera), Qelbree is a selective norepinephrine reuptake inhibitor (SNRI). These drugs join the extended-release (Ritalin LA) and immediate-release (Ritalin SR) methylphenidate, and guanfacine extended-release (Intuniv) as options for families who do not feel comfortable giving children Schedule II stimulants or for patients for whom substance abuse is a concern.

Like other SNRIs used to treat depression, Qelbree and Strattera carry black-box warnings about an increase in suicidality in the first months of treatment, particularly among teenage patients. Psychiatrists should remember that many drugs carry this warning and treatment benefits may well outweigh the risks. Antidepressants show a 2% greater incidence of suicidality than placebo, and use of these medications has been not associated with successful suicide attempts.

However, these medications are generally less effective than stimulants in treating ADHD. Patients who are not responsive to either stimulants or nonstimulants alone may be helped by combination therapy.

### Devices and Digital Therapeutics

The FDA has also recently approved 2 devices for treatment of ADHD in children. Clinicians should note that the standard for FDA approval is lower for devices than for drugs. Although drugs must prove both safety and efficacy, devices need only prove safety.

The first device is the Monarch external Trigeminal Nerve Stimulation (eTNS) System, a trigeminal nerve stimulator. Unlike the vagal nerve stimulator used to control epileptic seizures, this therapy does not require surgical insertion. The trigeminal nerve stimulator sits on the face. A small-scale study using data from the device manufacturer suggests that about half of pediatric ADHD patients responded to use of this device.

In the digital therapeutics category, the FDA has also approved use of a video game called EndeavorRx to treat ADHD. The sensory stimulus and motor challenges of the game target the neural pathways that govern focus and attention. Studies sponsored by the device’s manufacturer suggest that the prescribed use of the game improves attention and has few adverse effects.

Either or both of these devices may prove to be valuable adjuncts to medication and behavior management. More evidence of effectiveness would be helpful in guiding clinical decisions.

### Side Benefits of the Pandemic

One of the most important developments in ADHD treatment is not a device or medication, but the rise of telemedicine. Early in the COVID-19 pandemic, most large private insurance companies and the Centers for Medicare & Medicaid Services (CMS) waived the requirement that patients be seen in person—even when those patients are being started on Schedule II stimulants. Telehealth visits offer advantages, particularly when it comes to evaluating patients’ functional abilities. Some psychiatrists prefer to see children in their natural setting, where children are often quite a bit more hyperactive than they are in a doctor’s office.

Another odd benefit of the pandemic is that many children with ADHD have developed an increased appreciation for going to school. Patients with ADHD tend to struggle more with remote learning than their non-ADHD classmates. There are too many distractions at home, including the option of playing a video game while appearing to be in the virtual classroom. Most children with ADHD simply find it easier to concentrate when they are physically in school, and many patients with ADHD say they are glad to be back in school.

That is not something they would have expressed before the pandemic lockdown!

Dr Greenhill is a practicing child and adolescent psychiatrist in the San Francisco Bay area. As a member of the faculty of The REACH Institute, he co-leads the institute’s 3-day course that trains pediatric primary care providers to diagnose and manage common mental health conditions.

### REFERENCES

Lyme Disease in Psychiatry
Controversies, Chronic Symptoms, and Recent Developments
Jennifer Sotsky, MD, MS

Since its first appearance in a group of children in Old Lyme, Connecticut in the late 1970s, Lyme disease has proliferated throughout the United States and abroad. Only 30,000 to 40,000 cases are reported to the Centers for Disease Control and Prevention (CDC) per year, although recent studies looking at the time period between 2010 and 2018 estimate the actual number to be more than 10 times higher at approximately 476,000. Lyme disease is transmitted when an infected tick bites a human and injects the causative bacteria, *Borrelia burgdorferi*, into the skin. The majority of transmission in the United States occurs in the Northeast, mid-Atlantic, and upper Midwest, as shown in Figure 1.

While 70% to 80% of patients develop an erythema migrans rash, the majority of these rashes do not have the classic “bull’s-eye” appearance. Other patients may not recall seeing a rash and may have a flu-like illness with such mild symptoms that they do not seek medical attention. Left untreated, Lyme disease can cause wide-ranging effects, including arthritis, cranial nerve palsy, meningitis, depression, and cognitive impairment.

Even after appropriate diagnosis and antibiotic treatment, some patients continue to experience longer-term symptoms, including fatigue, cognitive dysfunction, and difficulty concentrating.

ACTIVITY GOAL
The goal of this activity is to better appreciate the controversies surrounding Lyme disease as well as methods to treat the neuropsychiatric sequelae.

LEARNING OBJECTIVES
• Understand the controversies surrounding Lyme disease diagnosis and treatment, including perspectives of different medical communities and patient communities
• Describe common neuropsychiatric presentations of and treatment options for Lyme disease and of posttreatment Lyme disease (PTLD)

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

ACCREDITATION/CREDIT DESIGNATION/FINANCIAL SUPPORT
This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of Physicians’ Education Resource®, LLC, and Psychiatric Times™. Physicians’ Education Resource®, LLC, is accredited by the ACCME to provide continuing medical education for physicians. Physicians’ Education Resource®, LLC, designates this enduring material for a maximum of 1.5 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This activity is funded entirely by Physicians’ Education Resource®, LLC. No commercial support was received.

OFF-LABEL DISCLOSURE/DISCLAIMER
This accredited CE activity may or may not discuss investigational, unapproved, or off-label use of drugs. Participants are advised to consult prescribing information for any products discussed. The information provided in this accredited CE activity is for continuing medical education purposes only and is not meant to substitute for the independent clinical judgment of a physician relative to diagnostic or treatment options for a specific patient’s medical condition. The opinions expressed in the content are solely those of the individual faculty members and do not reflect those of Physicians’ Education Resource®, LLC.

FACTORY, STAFF, AND PLANNERS’ DISCLOSURES AND CONFLICT OF INTEREST (COI) MITIGATION
The peer reviewer and staff members of Physicians’ Education Resource®, LLC, and Psychiatric Times™ have no relevant financial relationships with commercial interests.

None of the staff of Physicians’ Education Resource®, LLC, or Psychiatric Times™, or the planners or the authors of this educational activity, have relevant financial relationships to disclose with ineligible companies whose primary business is producing, marketing, selling, reselling, or distributing health care products used by or on patients.

For content-related questions, email us at PTEditor@mmhgroup.com. For questions concerning the accreditation of this CE activity or how to claim credit, please contact info@gotoper.com and include “Lyme Disease in Psychiatry: Controversies, Chronic Symptoms, and Recent Developments” in the subject line.

HOW TO CLAIM CREDIT
Once you have read the article, please use the following URL to evaluate and request credit: https://education.gotoper.com/activity/ptcm22jan. If you do not already have an account with PER®, you will be prompted to create one. You must have an account to evaluate and request credit for this activity.

Questions about this activity?
Call us at 877.CME.PROS (877.283.7767)
problems, or musculoskeletal pain in a condition known as posttreatment Lyme disease syndrome (PTLDS), sometimes also called posttreatment Lyme disease (PTLD). Studies suggest that approximately 10% to 20% of patients who are treated for Lyme disease with the recommended 2- to 4-week course of antibiotics continue to have nonspecific symptoms afterwards.\(^4\)

The Infectious Disease Society of America (IDSA), American Academy of Neurology (AAN), and American College of Rheumatology (ACR) published joint “2020 Guidelines for the Prevention, Diagnosis and Treatment of Lyme Disease”\(^4\) that included commentary on the terminology chronic Lyme disease, commonly used in the patient community, expressing concern that it lacks an accepted definition and is applied to a highly heterogeneous population who may have weak clinical or laboratory evidence to confirm prior infection with *B burgdorferi*. Although the IDSA had previously developed provisional criteria for the more specific subgroup of PTLDS, a term preferred by some researchers as it suggests a well-documented prior diagnosis of Lyme disease, they do not mention this term in their latest guidelines and instead refer to “persistent or recurring nonspecific symptoms such as fatigue, pain, or cognitive impairment following recommended treatment for Lyme disease.”\(^4\) There continues to be debate and conflict among patients, providers, and researchers about appropriate terminology for patients with chronic symptoms.

The Scope of the Problem and the “Lyme Wars”

There has been conflict and controversy surrounding Lyme disease since its earliest days. In 1970s Connecticut, mothers of children with unusual arthritis symptoms were angered due to feeling dismissed or ignored by public health officials after little was initially done when they told the officials of this unusual clustering of children with arthritis. In the decades following, intense disagreement continued among professional organizations, community doctors, and patients about what is required for a diagnosis of Lyme disease and what constitutes adequate treatment. The most pressing debates today involve how to treat PTLDS.

The recent joint IDSA/AAN/ACR guidelines recommend against repeat antibiotic treatment for patients with persistent or recurring nonspecific symptoms (eg, fatigue) who do not have objective evidence of reinfection with *B burgdorferi* or treatment failure (Table 1).\(^4\) The guidelines define objective evidence of persistent infection or treatment failure as signs of disease activity such as arthritis, meningitis, or neuropathy.

Beyond the Rash: Signs and Symptoms

Lyme disease can develop after an infected *Ixodes scapularis* tick bites human skin. Usually, at least 36 hours, and sometimes up to 72 hours of attachment is required to transmit the infection. Notably, *Ixodes scapularis* ticks may also transmit other infections, including *Babesia microti*, *Anaplasma phagocytophilum*, *Borrelia miyamotoi*, and others. In 70% to 80% of Lyme cases, an *Ehrlichia* migrans rash will develop at the site of the bite, often within 3 to 32 days.\(^5\) The rash typically starts as a red patch, that measures approximately 2 or more inches in diameter. This rash is not painful, but it expands over time and may have satellite rashes. As it grows, the initial patch may develop a central clearing, giving it a classic bullseye appearance (Figure 2). Most often, Lyme disease rashes do not have the bull’s-eye appearance and a significant percentage of patients do not recall having a rash at all.

Dissemination of infection beyond the initial localized area can result in a multitude of other symptoms in the following weeks to months. Because the initial immunologic response to Lyme disease involves the release of cytokines, many patients will experience moderate to severe flu-

---

**Table 1. Guidelines for Antibiotic Treatment of PTLDS (Summary)**

<table>
<thead>
<tr>
<th>2020 IDSA/AAN/ACR Joint Guidelines(^4)</th>
<th>2014 ILADS Guidelines(^5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>For patients who have persistent or recurring nonspecific symptoms such as fatigue, pain, or cognitive impairment following recommended treatment for Lyme disease, but who lack objective evidence of reinfection or treatment failure, IDSA/AAN/ACR recommends against additional antibiotic therapy.</td>
<td>ILADS recommends antibiotic retreatment when a chronic Lyme infection is judged to be a possible cause of the ongoing manifestations and the patient has an impaired quality of life.</td>
</tr>
</tbody>
</table>

---

**CASE VIGNETTE**

“Christina,” aged 45 years, is a mother of 2 children who presented reporting several months of low mood, fatigue, subjective memory problems, and headaches. She tearfully explained that she had chronic Lyme disease, commonly used in the patient community, expressing concern that it lacks an accepted definition and is applied to a highly heterogeneous population who may have weak clinical or laboratory evidence to confirm prior infection with *B burgdorferi*. Although the IDSA had previously developed provisional criteria for the more specific subgroup of PTLDS, a term preferred by some researchers as it suggests a well-documented prior diagnosis of Lyme disease, they do not mention this term in their latest guidelines and instead refer to “persistent or recurring nonspecific symptoms such as fatigue, pain, or cognitive impairment following recommended treatment for Lyme disease.”\(^4\) There continues to be debate and conflict among patients, providers, and researchers about appropriate terminology for patients with chronic symptoms.

The recent joint IDSA/AAN/ACR guidelines recommend against repeat antibiotic treatment for patients with persistent or recurring nonspecific symptoms (eg, fatigue) who do not have objective evidence of reinfection with *B burgdorferi* or treatment failure (Table 1).\(^4\) The guidelines define objective evidence of persistent infection or treatment failure as signs of disease activity such as arthritis, meningitis, or neuropathy.

Beyond the Rash: Signs and Symptoms

Lyme disease can develop after an infected *Ixodes scapularis* tick bites human skin. Usually, at least 36 hours, and sometimes up to 72 hours of attachment is required to transmit the infection. Notably, *Ixodes scapularis* ticks may also transmit other infections, including *Babesia microti*, *Anaplasma phagocytophilum*, *Borrelia miyamotoi*, and others. In 70% to 80% of Lyme cases, an *Ehrlichia* migrans rash will develop at the site of the bite, often within 3 to 32 days.\(^5\) The rash typically starts as a red patch, that measures approximately 2 or more inches in diameter. This rash is not painful, but it expands over time and may have satellite rashes. As it grows, the initial patch may develop a central clearing, giving it a classic bullseye appearance (Figure 2). Most often, Lyme disease rashes do not have the bull’s-eye appearance and a significant percentage of patients do not recall having a rash at all.

Dissemination of infection beyond the initial localized area can result in a multitude of other symptoms in the following weeks to months. Because the initial immunologic response to Lyme disease involves the release of cytokines, many patients will experience moderate to severe flu-
Although psychiatric problems can arise during the illness course, it is important to communicate to patients that most psychiatric symptoms in the general population are unrelated to Lyme disease. Treatment of such potentially disabling psychiatric disorders should not be delayed while trying to determine whether or not a patient has Lyme disease. Patients with preexisting anxiety may catastrophize and hyper-focus on information from the media that presents the most frightening consequences of their possible Lyme disease. It may be helpful to explain that whether or not a patient has Lyme disease, treatment of any cooccurring psychiatric disorder, such as major depression or panic disorder, is an essential part of the path to health.

It is also important to note that anchoring to Lyme disease early on, to the exclusion of consideration of other possibilities, can delay diagnosis of other serious medical conditions. The differential diagnosis for neuropsychiatric Lyme disease and PTLD is wide and includes other tick-borne diseases, psychiatric disorders, autoimmune disease, multiple sclerosis, sleep disorders, fibromyalgia, and others. A 2015 case series published in *JAMA Internal Medicine* described patients who were misdiagnosed as having persistent symptoms after Lyme disease, but actually had different malignancies, including pituitary adenoma and Hodgkin’s lymphoma. Thus, ensuring that patients have had a thorough medical evaluation and follow-up is critical.

### The Types and Limitations of Testing

The ideal diagnostic test for Lyme disease would clearly indicate the presence of *B burgdorferi* and activity or resolution of infection. Unfortunately, available tests fall short of this ideal, leading to conflict over diagnosis and treatment.

Two commonly available blood tests for Lyme disease are the ELISA and Western blot assay. The ELISA is an inexpensive, widely available, quantitative assay that reflects the magnitude of the antibody response (IgM and IgG) to spirochetal proteins. The Western blot assay (IgM and IgG) is an antibody-based test that detects binding of serum antibodies to an array of *Borrelia* antigens; it previously required interpretation by a skilled laboratory technician, but more recent developments have allowed interpretation by optical scanners. The IgG Western blot is considered highly specific for confirmation of current or past infection with *B burgdorferi*, while the IgM Western blot is less specific and may result in false positives.

In the 1990s, the CDC recommended a 2-tier testing approach to enhance diagnostic standards (Figure 3). The first step involves ordering an ELISA or immunofluorescence assay (an older test that now is less commonly used). If negative results are obtained, no further testing is recommended. If positive or equivocal results are obtained, then the Western blot assay is ordered. A positive result of the Western blot assay supports diagnosis of Lyme disease. A negative result does not necessarily rule it out, as early antibiotic treatment can abrogate the immune response or the assay may have been conducted too early, before the 2 to 3-week interval required for antibody development.

A central problem, therefore, in the 2-tiered method is that sensitivity varies considerably depending upon how early in the course of infection a patient is tested and on the specific manifestations of Lyme disease. Studies suggest that sensitivity of the 2-tier approach in early Lyme disease is poor, and only 29% to 45% of patients with Lyme disease will test positive; many may have false-negative assay results, such as early on in Christina’s case. Although sensitivity is excellent for Lyme arthritis, it is lower in disseminated neurologic conditions related to Lyme disease. Equally problematic is that a patient may test positive on an antibody test due to past exposure, and a positive test does not indicate treatment failure. The newer C6 ELISA and VlsE/pepC10 ELISA have improved sensitivity, although they are still far from ideal. In 2019, the CDC updated its recommendation to allow a second enzyme immunoassay, such as the C6 ELISA or VlsE/pepC10 ELISA, to be a reasonable substitute for the Western blot assay.

For suspected neurologic Lyme disease, lumbar puncture is indicated. In central neurologic Lyme disease, CSF analysis typically shows elevated...
lymphocyte and protein levels with normal glucose levels. Comparing the ratio of antibody levels in the CSF to blood collected on the same day allows determination of the intrathecal index which can provide strong evidence in support of the diagnosis of neurolytic Lyme disease. The presence of B burgdorferi DNA on polymerase chain reaction testing is also strong evidence for Lyme disease; however, this test has substantial rates of false negatives among patients with neurolytic Lyme disease and thus should not be used to disqualify a patient for antibiotic treatment. Structural and functional MRI as well as single-photon emission computed tomography and positron emission tomography scans have been used adjunctively to aid in diagnosis, but they are not sensitive or specific and may be costly or impractical in some clinical settings.

Neuropsychological testing may be helpful in supporting a diagnosis or measuring response to treatment, with studies showing the most consistently identified deficits in adults with Lyme disease to be problems with verbal memory, information processing speed, and memory-related tasks. However, this too can be costly and it yields nonspecific results.

Given the limitations of available tests, diagnosis for Lyme disease must be made considering factors such as the patient’s history of tick exposure, time spent in Lyme disease-endemic areas, clinical symptoms, and laboratory findings. Exciting developments are underway in Lyme disease testing, such as urine-based proteomic assays, blood-based metagenomic assays, and point of care tests, that hopefully will improve diagnostic accuracy and reduce delays in the provision of treatment.

**Treatment of Lyme Disease and PTLDS**

Because the diagnosis of Lyme disease is easy to confirm when the erythema migrans rash is present, the research community previously focused its efforts on studying the treatment of early Lyme disease; there have been fewer controlled studies of the later manifestations. Treatment of erythema migrans in adults includes a 10-day course of doxycycline or a 14-day course of cefuroxime or amoxicillin. This results in remission and apparent cure in most cases. Adults with Lyme arthritis can be treated with 28 days of oral doxycycline or amoxicillin. If joint swelling and pain persist, additional antibiotic therapy is recommended with 2 to 4 weeks of IV ceftriaxone. Acute neurologic Lyme disease (including Lyme-disease associated meningitis, cranial neuropathy, radiculoneuropathy, or other peripheral nervous system manifestations) and Lyme-related heart disease requires 14 to 21 days of IV ceftriaxone, cefotaxime, penicillin G, or oral doxycycline. IV antibiotic therapy is preferred for patients hospitalized with Lyme carditis. IV antibiotic therapy is also recommended over oral antibiotics when parenchyma of the brain or spinal cord is involved. The above treatment recommendations are based on the 2020 guidelines created by the IDSA, AAN, and ACR. The ILADS treatment guidelines for Lyme disease differ in general by recommending somewhat longer courses of antibiotic treatment.

When Lyme-triggered symptoms return or persist despite the standard antibiotic recommendations, considerable controversy arises over how to treat these patients. Approximately 10% to 20% of patients treated for Lyme disease have symptoms that can last for more than 6 months and even years after treatment. Common symptoms include muscle and joint pains, brain fog, fatigue, and sleep disturbance. Such symptoms cause significant distress and functional disability.

There have been 4 controlled studies of repeated antibiotic therapy for patients with PTLDS in the United States. In 2001, Klemper et al conducted 2 studies (1 for Lyme seropositive patients and 1 for seronegative individuals) randomizing patients to either 1 month of IV ceftriaxone followed by 2 months of oral doxycycline or IV placebo followed by oral placebo. Ultimately, no difference was found on the self-reported functional disability outcome measure between the antibiotic and placebo groups. The authors also noted that the treatment itself can cause significant risk, such as blood clotting. In 2003, Krupp et al randomized patients with persistent fatigue after treatment of well-documented Lyme disease to either 1 month of IV ceftriaxone or IV placebo, each followed by 5 months of no treatment. Those who received ceftriaxone were significantly more likely than those given placebo to be judged as responders on the fatigue measure at 6 months (69% vs 23%, respectively; P < .01).

However, somewhat surprisingly, the authors recommended against retreatment, likely due to the risk of serious adverse events associated with IV antibiotics. In 2008, Fallon et al randomized patients with Lyme encephalopathy to 10 weeks of IV ceftriaxone or placebo. There was overall greater cognitive improvement in the drug-treated group that was apparent at 3 months compared with the placebo group (P = .053), but this improvement was not sustained to 6 months. The authors argued that better treatments resulting in sustained cognitive improvement are needed. When the study was reanalyzed using the methods employed by Krupp et al in their fatigue study, very similar significant findings were found—nearly two thirds showed clinically meaningful reduction in fatigue after IV ceftriaxone compared to only 25% on IV placebo. Interpretation of these 4 studies has varied significantly from the IDSA/AAN/ACR guidelines, which largely recommend against retreatment with antibiotics for patients with PTLDS, to ILADS and others who argue retreatment should be considered for debilitating fatigue, as the only randomized controlled trial designed to assess fatigue found significant and clinically meaningful improvement on the primary fatigue outcome measure.

Several hypotheses exist to explain persistent symptoms after treatment for Lyme disease. One hypothesis is that such symptoms may represent an immune response to persistent infection with B burgdorferi. To date, multiple studies in animals have shown that B burgdorferi spirochetes can persist following standard recommended antibiotic treatment of a disseminated infection. Less often, case studies in humans have documented persistent bacteria, though it remains unclear whether these spirochetes are metabolically active or causing clinical disease. Other hypotheses include postinfectious processes that result in ongoing immune dysregulation, neural network dysregulation such as central sensitization, and...
preexisting vulnerability to anxiety and somatization.9 However, the exact cause of persistent symptoms is still not well understood, may be complex and multifactorial, and likely differs depending on the patient. A thorough medical evaluation to rule out tick-borne coinfections such as Babesia microti or Borrelia miyamotoi and other unrecognized comorbid medical or psychiatric problems is essential.

Patients with persistent symptoms after Lyme disease treatment may find that their family, friends, and doctors start to question why they still have symptoms, sometimes leading them to feel hurt, disbelieved, and defensive. Ironically, some of the problems typical of PTLDS may well be “in the head” as a result of neural changes induced by the Lyme disease infection or due to the stress and trauma associated with having a relapsing remitting illness. It is, therefore, important to guide patients in considering a trial of therapeutic strategies and to recognize brain- and symptom-focused treatments (eg, use of a serotonin-norepinephrine reuptake inhibitor for depression and pain, psychotherapy for interpersonal and other issues, graded exercise to address deconditioning, CBT and/or medications to improve sleep) that may have direct healing effects on the body.

There is no specific proven treatment for PTLDS at this time, but many patients find that typical treatments offered by psychiatrists can result in decreased pain, increased energy, better typical treatments offered by psychiatrists can result in decreased pain, increased energy, better quality of life. Additional research is underway internationally to better understand this complex illness, enhance diagnostic accuracy, and improve treatment outcomes.4

Concluding Thoughts

Lyme disease is a growing public health problem in the United States. If a sensitive and reliable test of active infection were available, much of the conflict around diagnosis and treatment would be diminished. This is the holy grail that scientists continue to seek. It is important to remember that symptoms of PTLDS (eg, fatigue, head/body aches, sleep difficulties, low mood, irritability, memory problems) can overlap substantially with those of common psychiatric disorders. The treatment approach should be based on the cause—persistent infection, postinfectious factors, or another more likely diagnosis. When psychiatric features are present, the psychiatric care should be optimized to enhance the likelihood of reduced suffering and optimal outcome. As a clinician, you should approach patients with PTLDS or chronic Lyme disease symptoms with humility and compassion, assuming they have been disbelieved by many. Advocate for additional medical workup when appropriate and treat their symptoms with appropriately targeted therapies.

Dr Sotsky is a fellow in consultation-liaison psychiatry at Columbia University Irving Medical Center with a part-time private practice; she formerly was a chief resident at Columbia’s psychiatry residency program. She is co-author of Conquering Lyme Disease: Science Bridges the Great Divide.

REFERENCES


Suggestons for Further Reading


Posttest, credit request forms, and activity evaluations must be completed online at https://education.gotoper.com/activity/ptcm22jan (requires free account activation), and participants can print their certificate or statement of credit immediately. This website supports all browsers. For PER’s privacy policy, please visit https://www.gotoper.com/privacy.

PLEASE NOTE THAT THE POSTTEST IS AVAILABLE ONLINE ONLY ON THE 20TH OF THE MONTH OF ACTIVITY ISSUE AND FOR 18 MONTHS AFTER.

Need Additional CE Credit? Check Out These Free CE Activities

Between Stoned and a Hard Place? Navigating Cannabis Medicolegal Issues
Chandler Hicks, DO; Maria Lapchenko, DO; Adrienne Saxton, MD; and Sara West, MD
Expiration Date: April 20, 2022

Assessing Malingered Voice-Hearing
Joseph M. Pierre, MD
Expiration Date: March 20, 2022
www.psychiatrictimes.com/view/assessing-malingered-voice-hearing
Psychiatrists: We’re recruiting Medical Directors

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

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

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

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

Salaries and Benefits

- $323,004 - $383,916/year
- Flexible workweek options may be available
- Substantial continuing medical education
- Defined-benefit pension (subject to Safety Retirement)
- Medical, dental and vision benefits
- Private practice permitted
- Retiree healthcare
- Patient-centric; treatment first environment
- Relocation assistance may be available

We’re also hiring for Staff Psychiatry positions—contact us to learn more!

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

For more information, visit careers@dsh.ca.gov or call (916) 654-2609.
Neurodevelopmental Child/Adolescent Inpatient Psychiatry

The NEW CHA Center of Excellence for Child/Adolescent Inpatient Mental Health Care at Somerville will provide a continuum of patient- and family- centered care for diverse youth with mental health needs. Including specialized autism spectrum/ neurodevelopmental beds.

Salaries starting at $300,000 and Sign on Bonuses!

- Provide clinical care to patients during periods of inpatient/ partial hospitalization
- Develop and maintain comprehensive treatment plans
- Participate in teaching opportunities
- Work in a collaborative practice environment
- Fully integrated electronic medical record (Epic) and robust interpreter service

Submit CV’s to ProviderRecruitment@challiance.org. Visit CHAProviders.org for more information.

In keeping with federal, state and local laws, CHA policy forbids employees and associates to discriminate against anyone based on race, religion, color, gender, age, marital status, national origin, sexual orientation, relationship identity or relationship structure, gender identity or expression, veteran status, disability or any other characteristic protected by law.

The Behavioral Service Line at Northwell Health is recruiting for a

Vice Chairperson,
Staten Island University Hospital

We are seeking full-time, board-certified psychiatrist applicants with outstanding clinical and managerial skills who have a passion for leading, directing and developing an academically-oriented behavioral health center of excellence. The Vice Chairperson will provide senior oversight of hospital-based services at Staten Island University Hospital. The Vice Chair will work collaboratively with hospital and health system leaders to meet and exceed the departments organizational, clinical, operational, and financial goals. Responsibilities include clinician recruitment, education, supervision, strategic development, and process improvement initiatives.

Required Education and Experience

- M.D. or D.O. Degree, or equivalent, from an accredited institution (ACGME or foreign program that is similarly accredited)
- Completion of a Residency in Psychiatry with Board Certification.
- Minimum of three (3) years of clinical practice in psychiatric medicine and previous leadership experience
- Must be licensed as a physician in the State of New York
- Experience in a leadership role in a hospital department, preferably in a major medical center or health system, required.

For more information and to apply, qualified candidates should forward their CV to Alice Perkins, OPR@Northwell.edu
New York City Health + Hospitals/North Central Bronx

The Department of Psychiatry has 70 Adult and Geriatric Acute Inpatient Beds, a Partial Hospital Program, Psychiatric Emergency Service, Consultation-Liaison Service, an Adult Ambulatory Practice, and a community-based Assertive Community Treatment Program.

Openings available include:

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

- **Incentive Bonuses Available for Qualified Candidates/Providers!**
- **Moonlighting opportunities also available!**

- **Academic appointments at Albert Einstein College of Medicine offered!**
- **Proof of Covid-19 vaccination is required prior to hire.**

We offer a generous compensation package, along with unparalleled health benefits, opportunities for advancement, retirement plan, malpractice, Sponsorship for H1 & J1 Visas, and much more! For immediate consideration, please contact Joe Mastov – Physician Recruiter, at: Mastov@pagny.org, call 646-895-3875, or apply online at: www.pagny.org

---

**PSYCHIATRIC TIMES – Classifieds Section**

**Psychiatric Times** classifieds section and job board provides you with the exclusive opportunity to promote your products and services directly in the mental health space.

Through both digital and print placements on our website, e-newsletters and publication, you will be able to position your offerings to leading mental health professionals.

Jules Leo
(609) 495-4367
jleo@mmhgroup.com
R.O.A.D.S.
FOUNDATION

FT or PT Adult and Child-Adolescent Psychiatrist Position

The R.O.A.D.S. Foundation, Inc. was created by a psychiatric group to care for mentally ill patients besides providing outpatient medical and dental services to the communities we serve.

We have two community clinics in Long Beach and Compton in addition to mobile clinics.

The work is all outpatient 9 am - 5 pm.

We offer:

- Generous incentive compensation plan
- Moving expenses
- Full-time employment – pay is $300,000 plus benefits that includes health insurance for employee plus family
- Part-time employment – $175 per hour without benefits
- Loan repayment available for non-profit organization employees

We invite you to make a difference in the communities we serve.

Email resume to: sarevian@roadsfoundation.org and cclayton@roadclinic.org

For more information regarding our organization, please visit www.roadsfoundation.org

CPS

Realize Your Dream Freedom & Flexibility

Private Practice

Tele-Psychiatry or In-Person

Flexible Work Hours

Clinical Freedom

Unlimited Vacations

No Calls

100% Outpatient

HI Visa Welcome

Earn over $350K/Year

Benefits include:

- Malpractice Ins. 401K, Medical, Dental, Vision & LTD ins
- We are looking for Adult and Child Psychiatrists in San Francisco Bay Area
- Los Angeles/Orange County Area
- San Diego Area
- Sacramento Area
- Comprehensive Psychiatric Services
- Mansoor Zuberi, M.D.

Phone: 925-944-9711 F) 925-944-9709
dzuberi@psych-doctor.com

www.psych-doctor.com

COLORADO

VitalCore Health Strategies

VitalCore Health Strategies, is looking for a part-time Psychiatrist for our facilities at Warren County Jail in Lebanon, Ohio and at Jefferson County Detention Facility in Golden, Colorado. The schedule is 4 hours per week and the days are negotiable. Clinical care can be given through telepsych or a combination of telepsych and on-site coverage. This position would serve as the collaborating Physician. There will also be coverage through a Psychiatric APRN.

Please contact Morgan Garrett MGarrett@VitalCoreHS.com

MASSACHUSETTS

CAPE COD

Cape Cod Healthcare


Cape Cod Healthcare

Cape Cod, Massachusetts

Live and Work Oceanside

New Inpatient/Outpatient Opportunity - Immediate full time opening for BC/BE Adult and/or Geriatric psychiatrist.

40 hour-per-week position in our outpatient clinic in Hyannis, MA every other week and our inpatient 20-bed locked unit the alternating week.

Schedule is Monday through Friday. Must also work one weekend on-call (twice a month). No weekend on-call duty is required but available if interested with extra compensation attached. Inpatient responsibilities include: timely evaluation of half of the inpatient unit census. You will be working with another psychiatrist in the unit as well as a psych APRN.

Outpatient responsibilities include: evaluations and follow-up appointments for psychiatric patients requiring medication management. Consultation/collaboration with other clinical staff on shared cases as needed.

*Potential to be a full inpatient position if interested

This will be an employed position by Cape Cod Healthcare with a generous base salary, sign-on bonus, and relocation support.

Please take some time to look at the Cape Cod Healthcare website at https://www.capeddhealth.org/medical-services/behavioral-health/

Enjoy coastal living at its best! Miles of sandy beaches for your enjoyment, quaint villages, and beautiful sunsets over Cape Cod Bay make this a great place to practice medicine and enjoy the amenities the Cape has to offer. It is truly a wonderful place to live and work.

If you are interested in speaking further about our position, please email me your CV and the best daytime you are available to talk.

Jolia Georges, Director of Physician Recruitment

Phone: 508-862-5481

jgeorges@capecodhealth.org

Hackensack Meridian Health

Hackensack Meridian Health is a leading not-for-profit health care network in New Jersey offering a complete range of medical services, innovative research, and life enhancing care aiming to serve as a national model for changing and simplifying health care delivery through partnerships with innovative companies and focusing on quality and safety.

The School of Medicine will be the cornerstone of a dynamic venue for the exchange of ideas, the development of healthcare and research thought leaders and practitioners, and the discovery of novel therapies to meet the medical challenges of the future.

“Ocean Medical Center’s psychiatry program will be a community-based program,” said Ramon Solhkhah, M.D., program director for psychiatry as well as founding Chair of Psychiatry & Behavioral Health at the Hackensack Meridian School of Medicine at Seton Hall University. “Our new psychiatry residency program will improve clinical care and ultimately encourage future health care leaders to build practices in the Jersey Shore area.”
UMass Memorial Health and the University of Massachusetts Medical School currently have openings within the Department of Psychiatry.

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

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

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

UMass Medical School

Area Medical Director, Department of Mental Health Office of Inpatient Management (Bostion, MA): provide administrative and clinical oversight for the DMH operated facility-based service system statewide.

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

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

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

Forensic Psychologist (Worcester Recovery Center and Hospital, Worcester, MA): Provides evaluations of competence to stand trial, criminal responsibility, civil commitment, and aid-in-sentencing.

Geriatric Researcher, Psychologist/Psychiatrist (UMMS, Worcester, MA): For additional information on the above, please contact: Marie Hobart, MD, Vice Chair, Public Sector Psychiatry marie.hobart@umassmed.edu

Interested applicants should apply directly at https://academicjobsonline.org/ajo/UMASSMED/Psych

(3-1 and 1-1/2 candidates are welcome to apply)

UMass Memorial Health Care

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

(2) Associate Medical Director, CHL (Worcester and North County MA): Provide psychiatric and medical supervision

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

Inpatient Psychiatrist, PTRC (Worcester, MA): Provide psychiatric services to mental health and substance abuse treatment to a 26-bed locked unit.

FT Clinical Rotating Adult Attending Psychiatrist (Worcester, MA): flexibility in clinical care, ranging from inpatient to emergency mental health services.

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

http://jobs.jobvite.com/umassmemorialmedicalgroup/physicians/search?q=Psychiatry

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

NORTH CAROLINA

CAPE FEAR VALLEY HEALTH

We Want You to Join Our Behavioral Health Team!

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

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

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

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

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

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

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

OHIO

VitalCore Health Strategies

Redefining healthcare

VitalCore Health Strategies, is looking for a part-time Psychiatrist for our facilities at Warren County Jail in Lebanon, Ohio and at Jefferson County Detention Facility in Golden, Colorado. The schedule is 4 hours per week and the days are negotiable. Clinical care can be given through telepsych or a combination of telepsych and on-site coverage. This position would serve as the collaborating Physician. There will also be coverage through a Psychiatric APRN.

Please contact Morgan Garrett MGMarrett@VitalCoreHS.com

WASHINGTON

Practice for sale

Large well established contract based long term care psychiatric practice in Seattle-Tacoma area.

Particular interest in geriatric and neurological psychiatry required.

IM plus annual earning potential while enjoying flexible hours and PNW lifestyle. MD owner would necessarily be present for transition period of at least a year.

Please contact: llenrow2@icloud.com

Find What You’re Looking For Now

Log on to ——

PsychiatricTimes.com/classifieds
to view our extensive list of jobs
Rethink Classifieds with Psychiatric Times™

*Psychiatric Times™* classifieds section and job board provides you with the exclusive opportunity to promote your products and services directly in the mental health space.

Through both digital and print placements on our website, eNewsletters and publication, you’ll be able to position your offerings to leading mental health professionals.

Contact us today to partner in meeting your promotional needs:

**Jules Leo**  
Sales Manager  
(609) 495-4367  
jleo@mmhgroup.com
LOREEV XR™ (lorazepam) extended-release capsules

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Please consult Full Prescribing Information before use.

WARNING: CONCOMITANT USE WITH OPIOIDS; ABUSE, MISUSE, ADDICTION; and DEPENDENCE AND WITHDRAWAL

Concomitant use with opioids may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant use for patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation.

LOREEV XR exposes users to risks of abuse, misuse, and addiction, which can lead to overdose or death. Abuse and misuse commonly involve concomitant use of other medications, alcohol, and/or illicit substances, all of which are associated with an increased frequency of serious adverse outcomes. Before prescribing LOREEV XR and throughout treatment, assess each patient’s risk for abuse, misuse, and addiction.

Continued use of LOREEV XR may lead to clinically significant physical dependence. The risks of dependence and withdrawal increase with longer treatment duration and higher daily dose. Abrupt discontinuation or rapid dosage reduction of LOREEV XR after continued use may precipitate acute withdrawal reactions, which can be life-threatening. To reduce the risk of withdrawal reactions, use a gradual taper to discontinue LOREEV XR, or reduce the dosage.

INDICATIONS AND USAGE

LOREEV XR is indicated for the treatment of anxiety disorders in adults who are receiving stable, evenly divided, three times daily dosing with lorazepam tablets.

DOSE AND ADMINISTRATION

Recommended Dosage

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

Administration Information

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

Dosage Increase for Inadequate Clinical Response

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

Discontinuation or Dosage Reduction

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

Concomitant Use with UDP-glucuronosyltransferase (UGT) Inhibitors

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

CONTRAINDICATIONS

LOREEV XR is contraindicated in patients with:

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

WARNINGS AND PRECAUTIONS

Dependence and Withdrawal Reactions

Acute Withdrawal Reactions

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

Promotred Withdrawal Syndrome

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

Central Nervous System (CNS) Depression

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

Patients With Depression or Psychosis

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

Risk of Paradoxical Reactions

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

Allergic Reactions to FD&C Yellow No. 5

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

Neonatal Sedation and Withdrawal Syndrome

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

Risk in Patients With Impaired Respiratory Function

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

Laboratory Tests

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

ADVERSE REACTIONS

In a sample of approximately 3,500 patients treated for anxiety, the most frequent adverse reactions to lorazepam tablets were sedation (15.9%), dizziness (6.9%), weakness (4.2%), and unsteadiness (3.4%).

The incidence of sedation and unsteadiness increased with age. The following reported adverse reactions are categorized by System Organ Class (SOC):

- Blood and Lymphatic System Disorders: agranulocytosis, leukopenia, pancytopenia, thrombocytopenia;
- Endocrine Disorders: SIADH;
- Eye Disorder: eye function/visual disturbance (including diplopia and blurred vision);
- Gastrointestinal Disorder: constipation and gastrointestinal symptoms, including nausea;
- General Disorders and Administration Site Conditions: asthenia, fatigue, hypothermia;
- Hepatobiliary Disorders: jaundice;

(Cont’d)


**Immune System Disorders:** anaphylactoid reactions, hypersensitivity reactions;

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

**Metabolism and Nutrition Disorders:** change in appetite, hyponatremia;

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

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

**Reproductive System and Breast Disorders:** impotence;

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

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

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

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

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

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Risk Summary**

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

**Lactation**

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

**Pediatric Use**

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

**Geriatric Use**

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

**Hepatic Impairment**

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

**DRUG ABUSE AND DEPENDENCE**

**Controlled Substance**

LOREEV XR contains lorazepam, a Schedule IV controlled substance.

**Abuse**

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

• Concomitant use with opioids may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant use for patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation.
• Use of LOREEV XR exposes users to risks of abuse, misuse, and addiction, which can lead to overdose or death. Before prescribing and throughout treatment, assess each patient’s risk for abuse, misuse, and addiction.
• Abrupt discontinuation or rapid dosage reduction of LOREEV XR after continued use may precipitate acute withdrawal reactions, which can be life-threatening. To reduce this risk, use a gradual taper to discontinue or reduce the dosage.

CONTRAINDICATIONS
LOREEV XR is contraindicated in patients with:
• hypersensitivity to benzodiazepines or any ingredients in LOREEV XR
• acute narrow-angle glaucoma

WARNINGS AND PRECAUTIONS
Central Nervous System (CNS) Depression
• LOREEV XR may produce CNS depression. Caution against engaging in hazardous occupations or activities requiring complete mental alertness.
• Use alone and with other CNS depressants may lead to potentially fatal respiratory depression. Alcohol should be avoided, and other CNS depressants used with caution.

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

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

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

Neonatal Sedation and Withdrawal Syndrome
• LOREEV XR use during later stages of pregnancy can result in sedation and/or withdrawal symptoms in the neonate. Monitor neonates during pregnancy and labor for signs of sedation and withdrawal.

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

DRUG INTERACTIONS
Avoid initiation of UDP-glucuronosyltransferase (UGT) inhibitors. Dose reduction requires switching to lorazepam tablets for dose adjustment.

USE IN SPECIFIC POPULATIONS
Because of the potential for serious adverse reactions, breastfeeding is not recommended during treatment with LOREEV XR.

For additional safety information about LOREEV XR, visit loreevxrHCP.com for the LOREEV XR Full Prescribing Information.

LOREEV XR™ (lorazepam) Important Safety Information
LOREEV XR and the LOREEV XR logo are trademarks or registered trademarks of Almatica Pharma LLC. Almatica and the Almatica logo are trademarks or registered trademarks of Alvogen TM S.a.r.l.

© 2021 Almatica Pharma LLC. All rights reserved.


LOREEV XR and the LOREEV XR logo are trademarks or registered trademarks of Almatica Pharma LLC.