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

Alan D. Blotcky, PhD; Ronald W. Pies, MD; 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.
FROM THE EDITOR

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 intrauterine events to perinatal complications 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 2020.1 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 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...
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 2005 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. I look forward to the time when 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.4 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

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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.6 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 available 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 cardiologic 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 confluence 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.”7,8 Our limited understanding of 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”9 and “Epigenetics Collides With Pharmacogenomics.”10

Neuroplasticity

Our growing understanding of the circuits of the human brain provides yet another opportunity to appreciate that, rather than being a provoked organ at birth, which I 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.11 Abdallah et al demonstrated that patients who responded to ketamine showed an increase in global brain connectivity in the caudate, insula, and lateral prefrontal cortex.12

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 citizenry and cooperation, and a strong dose of humility.

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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 for a job. I want a real paycheck. 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 just was 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](image_url)


Merrill Rotter, MD, & Michael T. Compton, MD, MPH

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

- **Highly detrimental US societal problems**
  - Adverse childhood experiences
  - Discrimination or social exclusion
  - Exposure to violence
  - Criminal justice involvement

- **Immediate and global physical environment**
  - Adverse built environment
  - Neighborhood disorder
  - Pollution
  - Global climate change impact

- **Socioeconomic status and opportunities for accruing wealth**
  - Low educational attainment
  - Unemployment or job insecurity
  - Poverty and income inequality
  - Neighborhood poverty

- **Basic needs in terms of housing, food, transportation, and health care**
  - Housing instability
  - Food insecurity
  - Poor insecurity
  - Poor access to transportation
  - Poor access to health care
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 fulltime 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—too overwhelming. It takes 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.

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### TABLE. THE APA’S POSITION STATEMENT ON SOCIAL DETERMINANTS

| The American Psychiatric Association’s “Position Statement on Mental Health Equity and the Social and Structural Determinants of Mental Health” states: |
| The American Psychiatric Association: |
| Supports legislation and policies that promote mental health equity and improve the social and structural determinants of mental health, and mental health objects to legislation and policies that perpetuate structural inequities. |
| Advocates for the dissemination of evidence-based interventions that improve both the social and mental health needs of patients and their families. |
| Urges health care systems to assess and improve their capabilities to screen, understand, and address the structural and social determinants of mental health. |
| Supports medical and public education on the structural and social determinants of mental health, mental health equity, and related evidence-based interventions. |
| 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. |
| Urges psychiatry residency training directors and other psychiatric educators to use systematic approaches to teaching about structural and social determinants of mental health. |
| 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. |
| 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. |

**Author’s Note:** The table above is a summary of the APA’s position statement on mental health equity and the social and structural determinants of mental health.
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.1

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,2 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.3

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:

“Senator Brown” has been observed, on several occasions, walking unsteadily in public and slurring his speech. There are persistent rumors in the lay press that Senator Brown has a drinking problem. A mental health professional is asked by a television news reporter, “Doctor, can you comment on Senator Brown’s abnormal behavior? Do you think he is an alcoholic? Is he fit to do his job?”

Inappropriate response: “Based on his unsteady gait and slurred speech, it is my professional judgment that Senator Brown likely has a serious drinking problem. This could well impair his ability to carry out his functions as a senator and lead to some dangerous behaviors.”

Appropriate response: “I have not evaluated Senator Brown, so I do not want to speculate on his condition or mental capabilities. Certainly, when someone shows gait instability and slurred speech, I would want to have that person evaluated medically. The problem could be some type of intoxication, involving alcohol or some other substance. But these reported behaviors could also be consistent with a metabolic or neurologic disorder of some sort. For example, hypoglycemia and various postictal (i.e., following a seizure) states may be mistaken for alcohol intoxication.”

Whether the senator’s condition—whatever it may be—would impair his ability to carry out his duties or cause dangerous behaviors would require a careful neuropsychiatric examination.”

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

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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 psychiatric diagnosis is beyond the scope of this text, but a few general points should be emphasized. First, as a matter of fairness with regard to the patients involved, an appearance of objectivity by anyone providing psychiatric consultation is of utmost importance. Second, extreme caution in applying the revised Goldwater Rule should be exercised when considering public or political figures without violating the intent and spirit of the Goldwater Rule. To better understand and implement Annotation 7.3, it would be helpful for 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.

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5 Crypto Investing Rules for Busy Doctors » Jesse Proulxman & 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, how will you know if you are making the best investment moves? As prices fluctuate, you may feel like you should do something in response—but what exactly you should do may be puzzling.

Makara, the first automated crypto investment advisor registered with the Securities and Exchange Commission, has 5 key rules.

1 || Stick to your plan.
The crypto markets are very volatile, and you can expect many fluctuations. Although you cannot control the uncertainties and movements, you can dictate when and how much you invest. Be consistent, and focus on what you can control. Investors who chase c

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 Proulxman is the cofounder and CEO of Makara as well as the cofounder of Strix Leviathan, a crypto hedge fund. Prior to his work at Makara and Strix Leviathan, he served as an IBM Distinguished Engineer, focused on blockchain and cryptocurrency.

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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. Psychotherapy, 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 (ie, 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 pathoetiology, 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 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

FREDERICK CHARLES NUCIFORA JR, PHD, DO, MHS

SCHIZOPHRENIA 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 treatments and are therefore considered to have ultra-TRS (UTRS).4 30% of TRS patients do not respond to clozapine when designing studies.

Clinical Features

Analysis of clinical phenotype suggests that patients with TRS have an earlier age of onset than patients with non-TRS.7 Unlike non-TRS, the ratio of men to women with TRS is equal,7 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.9 Cognitive functioning, and particularly verbal memory, is more impaired in patients with TRS than with non-TRS.5,9,10 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.11 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 pharmacogenomic 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.11 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 polygenic risk scores (an index of overall genetic risk of developing a disease),12 a higher frequency of disruptive mutations,13 and higher rates of chromosomal duplications and deletions.14 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).15 Many of these studies have not yet been replicated, again likely a consequence of 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).16 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 (GYPIC).

Pathways associated with TRS included clathrin-mediated endocytosis, stress-activated protein kinase/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,12-17 possible white matter tract disruption,20 and disruptions of functional connectivity, particularly in frontotemporal grey matter.

Table 1. Findings in Comparing UTRS and TRS

<table>
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<th>UTRS is associated with:</th>
<th>N longer illness duration</th>
<th>Small anterior thalamic volume</th>
<th>Lower lower perfusion</th>
<th>Lower glutamate + glutamine in putamen</th>
<th>Higher higher anterior cingulate gyrus glutamate levels</th>
<th>Weaker network connectivity</th>
<th>Low-grade inflammatory inflammation</th>
</tr>
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</table>
poral networks, with direct and indirect involvement of the thalamus.\textsuperscript{23-25} 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{15,23,37}

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{30,31} a finding that was subsequently replicated.\textsuperscript{32} 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{30} 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{40} 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 that distinguish UTRS from TRS.\textsuperscript{33} 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{40} 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{41} Even for those receiving clozapine, the average delay from the point in time when clozapine would have been considered indicated is 48 months.\textsuperscript{42} Patients who might respond to clozapine are instead treated with multiple antipsychotics or high-dose antipsychotics. The underuse 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
can be monitored and mitigated, and data sug-
gest that patients are less bothered by mandatory
blood draws than prescribers tend to think and
prefer clozapine to other medications.44-46
There are a number of resources to help
prescribers wishing to use clozapine (Table 2).
Expanding
these programs and seeking advice from estab-
lished clozapine clinics, such as the one we have
at Johns Hopkins, and others across the country
could provide instruction and consultation.
Improving
the ease of the user and allowing some of
the Clozapine Risk Evaluation and Mitigation
Strategy registry restrictions could help address
the underutilization of clozapine.

Concluding Thoughts
These data suggest that subtype patients based
on treatment response (TRS or URS versus non-
TRS) could identify more homogeneous popula-
tions of patients with distinct differences in
pathophysiology. Understanding the mechanisms
leading to TRS and URS, and the difference
between the 2, may provide the opportunity to
develop biomarkers of disease state and treatment
response, and to develop novel treatments. Further,
the available data suggests that genetic, clinical,
and pathogenic studies will benefit by considering
treatment response as a variable. Finally, patients
with schizophrenia who do not respond well to
treatment suffer considerably and place great
stress on their families and the health care system.
Investment in research and services for this
group of patients is imperative.

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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 350.10,11

Limited effectiveness of both pharmacological and psychological treatments contributes to this chronicity. Family-based therapy, which works in alliance with parents to maintain eating and restore weight, has had some success in adolescent patients, but not all younger patients achieve adequate benefit. For older patients with AN, evidence-based therapies remain underdeveloped.

Historically, AN has been considered a consequence of psychosocial factors.1 However, considerable recent evidence supports powerful genetic and neurobiological contributions to AN behavior.2,3 Many affected individuals have an anxious, obsessive, inflexible, and perfectionist temperament that presents in childhood before the onset of AN, becomes exaggerated during illness, and persists in a mild-to-moderate form after recovery. Comorbid depression is common, as is denial of illness and lack of motivation to change.4

Recent studies have shed new light on underlying mechanisms driving such AN symptoms.5 For example, when people are hungry, activation of brain circuits normally makes them feel irritable and uncomfortable and makes food more rewarding 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

Despite these limitations, expert articles and guidelines most likely recommend olanzapine as the antipsychotic of choice to treat AN, because so few RCTs 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.

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.13 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 2019.14 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

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 heights 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.15-17 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—along with most other current atypical antipsychotics, including quetiapine and risperidone—is a 5-HT2/D2 antagonist. Aripiprazole, in contrast, is a D4 and 5-HT1a partial agonist, meaning it acts differently at dopamine and serotonin receptors. Theoretical arguments have addressed how use of aripiprazole at lower doses (typically 0.5 mg/d in some patients). Whether treatment of comorbid antidepressant augmentation is associated with higher morbidity among patients with AN, and comorbid psychiatric disorders are associated with higher mortality among patients with AN, population, use of medication to target these conditions is supported.10,11 Research has yet to establish the extent of symptoms in AN 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 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
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://kusterstekst.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 thought, writing, and life; and with affinities to the early works of the French existentialists, Sartre and Camus. What brings these works together is the focus on philosophical problems of good and evil, life and death, I and the other, without getting lost in academic reasoning for the sake of reasoning itself. It does not present a psychopathological theory, but it does focus on madness as a lived experience, as a concept in 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
assumed that there is a healthy, sane part, and an insane, psychotic part, both manifesting themselves in various contexts and intensities. Therapy then consists in identifying and annulling the psychotic part (eg, by medication, by cognitive behavioral therapy, or by so-called psychoeducation, and stimulating the healthy part). The patient then eventually learns to associate him- or herself with the healthy part, dissociate from the disordered part, and to consider the psychosis as the illness, not belonging to who he or she really is, but as something that was intruding from the inside. They learn to say: “the psychosis disturbed the real me.” Instead of: “the psychosis showed a different aspect of me.” It thereby dissociates them from their own experiences, memories, and past.

The assumption in much theory, and the accompanying practices, is that the life-world of the individual is affected by a natural disorder, which eventually impairs the individual in their freedom, in their meaningful interaction with others, and in their sense of being a conscious individual. What most of these accounts simply miss is that the psychotic experience itself is meaningful. Psychotic individuals often experience more freedom, instead of less, and they feel their consciousness is not troubled, but they report all kinds of experiences that are phrased with positive light metaphors. By defining psychosis as a certain lack, psychiatry and psychology imply that meaning, freedom, and truth are only found in the nonpsychotic way.

What philosophy has to offer here is an examination of both sides, an inquiry into those notions that are so often assumed to be absent in psychosis. Philosophy investigates the power and implications of the negative: for instance, in what world does the psychotics live, when it is claimed that s/he does not live in a real world? How is this supposed unreality experienced? Why does it often feel more real than so-called ordinary reality? And so on. Only by letting go of our own prejudices about reality and thought, about how language and meaning operate, may we gain a deeper understanding of other (psychotic) kinds of organizations, other kinds of being-in-the-world than that of the nonpsychotic individual.

I do not have any principled criticism of the use of medication or cognitive behavioral therapy in itself. But the pretension that often accompanies the provision of effective treatment, that the clinicians understand what psychosis is better than the persons themselves—that can have a negative impact on people’s lives. If psychosis were really just like diabetes or a broken leg, a temporary natural disturbance of the mind, why would so many remain so puzzled afterwards? What is this mysterious, seductive quality of psychosis? Psychosis is not only a disorder. It is also the basis for thinking toward a different order.

AFTAB: I have been wondering about the relationship between psychosis and philosophy. In my mind, one way to approach it would be to treat psychosis as a method of inquiry into the nature of reality such that, at the end of it, 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?

KUSTERS: 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 transience. 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 undeniable truth and givenness of one’s own existence. The argumentative structure in Descartes’ texts shows similarities with the existential doubts the madman is in.

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.

What most of these accounts simply miss is that meaning, freedom, and truth are only found in the nonpsychotic way. 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 festam. 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 website 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, antihumanist, 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-]extermination. 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 psychosis 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®.

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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.

Current Schizophrenia Treatment Approaches – Progress, but Unmet Needs Remains
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 D<sub>2</sub> 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 D<sub>2</sub> receptor but with a lower affinity, and added antagonism at serotonin 5-HT<sub>2a</sub> 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<sub>2</sub> 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 D<sub>2</sub> or 5-HT<sub>2a</sub> receptor antagonism. Studies have found that TAAR1 agonists can reduce the firing of dopaminergic and serotoninergic 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-HT<sub>1A</sub>) receptor 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, watch this short video: www.sunovion.com/taar1modvideo

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.

To watch a video explaining TAAR1 visit: www.sunovion.com/taar1modvideo

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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, 16% of the consultations were for delirium, yet delirium was diagnosed by the palliative care team in 56% of the patients.1

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.

TALES FROM THE CLINIC: THE ART OF PSYCHIATRY

SERIES EDITOR NIDAL MOUKADDAM, MD, PHD

Delirium: Don’t Miss It

Jennifer Howse, MD

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.

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...
Delirium can be related to cancer, its treatment (ie, radiation, chemotherapy), and non-cancer-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 a 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 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 delirious 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 remission 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 the 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 delirious patients recalled their delirium. Predictors of patients not recalling their delirium are greater “short-term memory impairment during the delirium episode, the severity of the delirium episode itself, and the presence of perceptual disturbances.” However, more severe hallucinations and delusions, corticosteroid-induced delirium, and poorer Karnofsky Performance Status (KPS) Scale scores were correlated with more delirium-related distress for patients. Caregivers are more likely to be distressed when the patient has a history of transition to a different opioid with the goal of 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 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 delirious 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 remission 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 the end of life have been associated with worse patient quality of life and worse bereavement in their caregivers.

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3 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.4-7 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.4-7 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.8 The efficacy of these tests in establishing optimal treatment is still being determined.9

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.10 The patient should be in steady state when taking samples, and samples should generally be taken 10 to 12 hours after the last dose was taken. If a drug level is outside the expected range, the patient may not be adherent or may not metabolize the drug as expected.

<table>
<thead>
<tr>
<th>Number of prior treatment failures</th>
<th>Remission rate</th>
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<tbody>
<tr>
<td>No or limited prior treatment</td>
<td>27.5%</td>
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<tr>
<td>1 prior failure</td>
<td>21.2%</td>
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<tr>
<td>2 prior failures</td>
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<tr>
<td>3 prior failures</td>
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2. **Failures and Remission Rate Between Prior Treatment**

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3. **Follow-Up**

For more information on psychiatric disorders, visit go/psych2021activity.
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, aripiprazole, cariprazine, lurasidone, 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 62.3% to 26.4%. 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.

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. Adherence to medications is also 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

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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 ongoing 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-refering 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
hand to pull away from that burner before your left side uses the words, “Hot! Pull back!”

The left catalogs time as a series of disconnected, static points and cannot follow or generate a narrative arc. It is self-conscious, bossy, resistant to change, and the source of that nasty inner voice creative people dub The Critic.

When writing an essay (or composing a piece of music, or setting up a scientific study, or bringing forth anything new) the right side creates the raw first draft, and the left then revises, edits, and polishes it. That revision process (left brain) may spark a new idea (right brain), which then needs further modification (left brain), which sparks another idea (right brain), and so on. This dance, called flow, is associated with a profound sense of wellbeing and aliveness.

When things are going well in treatment, the same kind of back and forth occurs between patient and clinician. Back to doorknob moments. The appointment is a narrative arc because it has a clear beginning, middle, and end. The patient’s function in the treatment relationship, like the right hemisphere’s, is to present raw material while tracking the time and figuring out how to close the narrative arc (both occur out of consciousness) as the end of the session (the deadline) approaches. One option is the cliffhanger, ie the bombshell disclosure. The clinician’s function, like the left hemisphere’s, is to analyze and think about the patient’s disclosure between sessions, and then use resulting insights to move the treatment forward. Thus, the last-minute bombshell serves both as the result of insights to move the treatment forward. Keep it safe for patients to deliver them by the deadline—somehow empowers them.

To keep revealing new material, patients need to trust us. They often break down after revealing the raw self; they are reassured to be reminded that it is part of the process.

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 prevent stagnation. 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. I can tolerate a great deal of patient distress if there is a sense of time guarantees a safe therapeutic environment and facilitates trust. I have found that most patients leave willingly and quickly after the disclosure—because they have done their job. Time to go. Patients use the bulk of the session time to work up to delivering the revelation (again, whether knowingly or unknowingly). They may not need, or even want, my immediate response, for various reasons, the most straightforward of which is simple fatigue. Overcoming resistance is exhausting.

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Artists who regularly birth new work know new work reveals new data against the left’s nay-saying. 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.

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Clinical Implications

Dropping a bomb is not without danger for the patient. Revealing the raw self makes them vulnerable. Once the revelation is out in public, it can never be private again. However, although risky and anxiety provoking, disclosure is necessary to prevent stagnation. 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.

To keep revealing new material, patients need to trust us. They often break down after revealing the raw self. Going with the hypothesis that they released the information because the session was ending, running over time sends patients undesirable, nonverbal messages: 1) we are unpredictable, therefore untrustworthy, and 2) we do not trust them to pull themselves together without us.

In the first, we violate the do-no-harm rule. Lack of predictability arouses anxiety and distrust. In the second, we collude with and/or foster codependence, and again violate the do-no-harm rule. The patient’s right brain notes this (again, out of conscious awareness) and may stop dropping bombs. If a treatment is stagnating, this may be why.

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.
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 schizophrenia 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 criteria. If mood syndromes were present longer than 2.5% of the time, the diagnosis would be schizoaffective disorder or bipolar with psychosis. However, the DSM-5 criteria for schizoaffective disorder offer the mirror image of the D criteria for schizophrenia. Here, the individual must meet criteria for a mood syndrome for the majority (ie, 50% or more) of the total time that they have been ill. In DSM-IV, it had to be substantial (ie, more than brief [2.5%]). Diagnosis also requires the other schizoaffective criteria, including 2 weeks of psychosis in the absence of prominent mood symptoms. Here, the term mood symptoms is used instead of syndrome, meaning that there cannot be any prominent symptoms—much less the full syndrome—of mania or depression present for those 2 weeks.

There seem to be very few patients who meet these DSM-5 criteria for schizoaffective disorder, which require that they be in a mania (or depression) for the majority of the time and also have psychosis without any significant symptoms of a mood disorder for 2 full weeks. Making it tougher to diagnose schizoaffective disorder was probably intended by the DSM-5 authors. The evidence they considered suggested that the disorder, as defined in DSM-IV, did not exist; “they wanted to eliminate it. They retained it because of pushback from field trials, with practicing psychiatrists who largely wanted to keep schizoaffective disorder in the manual.

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 schizophrenia, 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 pali-peridone 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 children1 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.2 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.3

Yet with such a high demand for doctors, there are only approximately 8900 practicing child psychiatrists in this country.4 At a time when health care professionals are stretched thin, access to child psychiatry5 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,”6 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 4 different kinds of mental health chatbots exist, mostly focused on treating depression or autism.7 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.8 The study authors wrote:

“The number of participants reporting that the bot felt empathy 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.9

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 medication 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 resiliency 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.10

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.

An estimated 7.7 million children1 have at least 1 mental health disorder, and half are not receiving the treatment they need.

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 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 self-reported caregiver strain after 3 weeks of treatment. Moreover, data presented by the manufacturer show that the effect of Jornay PM lasts through the school day and into the evening.

Nonstimulant Medication
In April 2021, the FDA approved vloxetine (Qelbree) for treatment of ADHD in patients aged 6 to 17 years. Like atomoxetine hydrochloride (Strattera), Qelbree is a selective norepinephrine reuptake inhibitor (SNRI). These drugs join the alpha-2 agonists (eg, clonidine hydrochloride extended-release [Kapvay], 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 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 tended 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 long-term symptoms, including fatigue, cognitive
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.3,4

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.

The International Lyme and Associated Diseases Society (ILADS) guidelines (Table 1) recommend “patients with persistent symptoms and signs of Lyme disease be evaluated for other potential causes before instituting additional antibiotic therapy”; however they advocate for “…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.” Some providers adhere to the more rigid IDSA/AAN/ACR guidelines and others follow the more flexible ILADS guidelines, sometimes leading to heated debate. Such debates have also involved patients and their advocates who can feel dismissed or disbelieved. Amid this charged climate that the media have referred to as the “Lyme wars,” physicians and patients alike can feel frightened, alienated, and overwhelmed.

Given the substantial overlap in symptomatology between Lyme disease and common psychiatric disorders, as well as the psychological effects that can result from a stigmatized illness, many psychiatrists will see patients with documented or suspected Lyme disease. It is important for psychiatrists to keep Lyme disease on their list of differential diagnoses, to be familiar with diagnostic and treatment strategies, and to understand the challenges patients and providers face due to this complex illness. The following case and text will highlight signs and symptoms to look for, as well as diagnostic strategies and management approaches for such patients.

### Table 1. Guidelines for Antibiotic Treatment of PTLDS (Summarized)

<table>
<thead>
<tr>
<th>2020 IDSA/AAN/ACR Joint Guidelines</th>
<th>2014 ILADS Guidelines</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 could barely function and reported feeling dismissed by her primary doctor. Christina briefly saw a therapist in college for stress related to a relationship breakup, but she otherwise had had no history of psychiatric treatment. She had a recent unreliable examination, including vitals and basic blood work, by her primary doctor, who referred her to the psychiatry department for depression.

Christina was started on sertraline 50 mg with some mild improvement in low mood, but had ongoing fatigue, memory issues, and headaches. On further discussion, you learned that 3 months prior, Christina visited family in Massachusetts for the July 4th holiday. She remembered returning from the party with a flu-like illness, but she tested negative for COVID-19 infection and on a Lyme enzyme-linked immunosorbent assay (ELISA) antibody test the following week. She did not recall having any tick bites or rashes. After you discussed the case with Christina’s primary doctor, he ordered a Lyme ELISA antibody test, which yielded positive results. She was then given a confirmatory immunoglobulin (IgG) -G Western blot test, which also yielded positive results.

Christina received treatment with a course of doxycycline and experienced improvement in her fatigue, headaches, and mood. Two months later, she returned with worsening fatigue and headaches. Looking to the IDSA/AAN/ACR guidelines, Christina’s primary doctor recommended against retreatment with antibiotics, as he felt there was no clear evidence of reinfection or persistent infection. Christina sought a second opinion from another community physician, who did additional lab testing—including cerebrospinal fluid (CSF) studies—to evaluate for tick-borne coinfections and autoimmune disease. Workup was unremarkable, but given her severe symptoms, she treated her with courses of doxycycline and amoxicillin, and at this time felt much better.

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 erythema migrans rash will develop at the site of the bite, often within 3 to 32 days.2 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 PTLDS 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 WBC count and elevated protein. The serum and CSF ELISPOT is a new test that can be used for confirmation of neurologic involvement.

### Table 1. Neurologic Conditions Related to Acute Lyme Disease

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>CHARACTERIZED BY</th>
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<tbody>
<tr>
<td>Meningitis</td>
<td>headaches, neck stiffness, light/sound sensitivity, nausea, vomiting or pain with eye motion</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>acute onset sleepiness, mood swings, irritability, personality change, cognitive problems</td>
</tr>
<tr>
<td>Cranial neuritis (eg, CNVI palsy or Bell Palsy)</td>
<td>unilateral or bilateral facial weakness or drooping</td>
</tr>
<tr>
<td>Radiculoneuritis</td>
<td>numbness, tingling, or pain (often described as sharp, stabbing, burning, or shooting) that radiates down along the nerves into the limbs or across the trunk</td>
</tr>
</tbody>
</table>

### Table 2. Flu-Like Symptoms During the Early Disseminated Phase of Lyme Disease

- Fatigue
- Loss of appetite
- Muscle and joint aches
- Swollen lymph nodes
- Fever
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 neurologic 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 neurologic 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 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, Klempner 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. 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 co-infections 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 cognition, and enhanced quality of life. Additional research is underway internationally to better understand this complex illness, enhance diagnostic accuracy, and improve treatment outcomes.

**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, 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**

The Call for Papers submission form will be available at www.aacap.org/AnnualMeeting-2022, and all submissions must be made online. Abstract proposals are prerequisites for acceptance of any presentation. Topics may include any aspect of child and adolescent psychiatry.

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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-B, J 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
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@roadfoundation.org and cclayton@roadclinic.org

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

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VitalCore Health Strategies

VitalCore Health Strategies, is looking for a part-time Psychiatrist for our facilities at Cape Cod Healthcare with a generous base salary, sign-on bonus, and relocation support.

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

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CLASSIFIEDS 37

DEPARTMENT OF PSYCHIATRY

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.

Through a partnership between Hackensack Meridian Health and Seton Hall University, the School of Medicine will redefine graduate medical education, research, and clinical practice; reverse the critical physician shortage in both the New York/New Jersey metropolitan area and the nation; and stimulate economic development in northern New Jersey.

The School of Medicine will be the anchor in the development of a comprehensive health sciences campus that will also include research facilities and biotechnology endeavors – all in service of educating tomorrow’s doctors, discovering novel therapies, and facilitating compassionate and effective healthcare that will meet the ever-changing needs of tomorrow’s patients.

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.”

As the area’s premier provider of psychiatric services, Hackensack Meridian Behavioral Health Services has provided comprehensive mental health and substance abuse services to the residents of Monmouth, Ocean, Middlesex, and Bergen Counties for over forty years. Due to continued growth and expansion, we are currently accepting applications for Psychiatrists to join our Mental Health and Addiction Interdisciplinary Teams in the following positions:

• Carrier Clinic - Staff Psychiatrist (Belle Mead, NJ)
• Consultation Liaison Psychiatrists: Raritan Bay Medical Center (Perth Amboy)
• Medical Director ED/Crisis: Jersey Shore University Medical Center (Neptune, NJ)
• Inpatient: Raritan Bay Medical Center (Perth Amboy, NJ)
• Outpatient: Ocean Medical Center (Brick, NJ) and (Manahawkin, NJ)
• Medical Director for Adult Inpatient Unit: Riverview Medical Center (Red Bank, NJ)
• Outpatient: Southern Ocean Medical Center (Manahawkin, NJ)
• Outpatient Child & Adolescent Psychiatrist: Hackensack University Medical Center (Hackensack, NJ)
• Geriatric Psychiatry: Hackensack University Medical Center (Hackensack, NJ)
• Telehealth Remote Psychiatrist FT/PT

Renee.Theobald@hmhn.org
or call: 908-839-5693
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 groups (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.

North Carolina

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 exceed the 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 EDV 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.

North Carolina State University (StateHires.com):

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, 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

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: lenrow2@icloud.com

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**Jules Leo**  
Sales Manager  
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jleo@mmhgroup.com
LOREEV XR™ (lorazepam) extended-release capsules
BRIEF SUMMARY OF PRESCRIBING INFORMATION
Please consult Full Prescribing Information before use.

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.

Protracted 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

Leukocytosis 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, disinorientation, 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 benzodiazepine 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 insufficient 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, disinorientation, 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.

Physical Dependence
LOREEV XR may produce physical dependence from continued therapy. Abrupt discontinuation or rapid dosage reduction or administration of flumazenil may precipitate acute withdrawal reactions, including seizures, which can be life-threatening.

Acute Withdrawal Signs and Symptoms
Acute withdrawal signs and symptoms associated with benzodiazepines have included abnormal involuntary movements, anxiety, blurred vision, depersonalization, depression, derealization, dizziness, fatigue, gastrointestinal adverse reactions (eg, nausea, vomiting, diarrhea, weight loss, decreased appetite), headache, hyperacusis, hypertension, irritability, insomnia, memory impairment, muscle pain and stiffness, panic attacks, photophobia, restlessness, tachycardia, and tremor. More severe acute withdrawal signs and symptoms, including life-threatening reactions, have included catatonia, convulsions, delirium tremens, depression, hallucinations, mania, psychosis, seizures, and suicidality.

Protracted Withdrawal Syndrome
Protracted withdrawal syndrome is characterized by anxiety, cognitive impairment, depression, insomnia, formation, motor symptoms (eg, weakness, tremor, muscle twitches), paresthesia, and tinnitus that persists beyond 4 to 6 weeks after initial benzodiazepine withdrawal. Protracted withdrawal symptoms may last weeks to more than 12 months.

Tolerance
Tolerance to LOREEV XR may develop from continued therapy.

OVERDOSAGE

Clinical Experience
In postmarketing experience, overdose with lorazepam has occurred predominantly in combination with alcohol and/or other drugs. Manifestations of overdose include varying degrees of CNS depression, ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion, paradoxic reactions, dysarthria, and lethargy. In more serious cases, symptoms may include ataxia, hypotonia, hypotension, cardiovascular depression, respiratory depression, hypnnotic state, coma, and death. In case of an overdose, consult a Certified Poison Control Center at 1-800-222-1222 for latest recommendations.

Distributed by:
Almatica Pharma LLC
Morristown, NJ 07960 USA
PI658-00

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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.

Risk in Patients With Impaired Respiratory Function
• Closely monitor patients taking LOREEV XR for impaired respiratory function, and consider discontinuing it if signs and symptoms of respiratory depression or apnea occur.

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 during long-term therapy.

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.

Please see the accompanying Brief Summary.

You are encouraged to report negative side effects of prescription drugs to Almatica at 1-877-447-7979 or the FDA at www.fda.gov/medwatch, or call 1-800-FDA-1088.