CLINICAL REFLECTIONS

Vaccine Mandate Exemptions for Anxiety: Ethical and Practical Considerations

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Many US health care institutions have established mandatory COVID-19 vaccination policies to protect employees, patients, and the community, as well as to comply with the Occupational Safety and Health Administration’s anticipated emergency temporary standard requiring health care providers with 100 or more employees to ensure that staff are vaccinated.1 In response, some health care workers are submitting vaccine exemption requests for religious, medical, and mental health reasons, and organizations are challenged with determining the validity of these requests with little precedent to inform current policy. The purpose of this article is to discuss how behavioral health (BH) experts in one organization conceptualized anxiety-related medical exemption requests for the COVID-19 vaccine, in an effort to inform others confronted with similar circumstances.

It is important to recognize that vaccine mandates for health care workers protect

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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.

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

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

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

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

Discontinuation or Dosage Reduction
To reduce the risk of withdrawal reactions, use a gradual taper to discontinue LOREEV XR, or reduce the dosage.

Concomitant Use with UGT-glucuronosyltransferase (UGT) Inhibitors
If a UGT inhibitor is initiated during treatment with LOREEV XR, discontinue LOREEV XR and switch to lorazepam tablets to reduce the dosage.

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

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

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

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

The incidence of sedation and unsteadiness increased with age. 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.
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, disorientation, 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 insufficiency and/or encephalopathy.

DRUG ABUSE AND DEPENDENCE

Controlled Substance
LOREEV XR contains lorazepam, a Schedule IV controlled substance.

Abuse
LOREEV XR is a CNS depressant with a potential for abuse and addiction. Even taking as prescribed may put patients at risk for abuse and misuse of their medication. The following adverse reactions have occurred with benzodiazepine abuse and/or misuse: abdominal pain, amnesia, anorexia, anxiety, aggression, ataxia, blurred vision, confusion, depression, disinhibition, disorientation, dizziness, euphoria, impaired concentration and memory, indigestion, irritability, muscle pain, slurred speech, tremors, and vertigo. The following severe adverse reactions have occurred with benzodiazepine abuse and/or misuse: delirium, paranoia, suicidal ideation and behavior, seizures, coma, breathing difficulty, and death. Death is more often associated with polysubstance use.
PUBLISHER’S NOTE

As we continue this new year, there are still many uncertainties. At press time, the omicron variant was causing a record number of cases, adding to the stresses of already taxed clinicians like yourself. In addition, this new wave continues to add to anxiety and disruptions in patients’ lives. Although we all wished we had turned the corner of the pandemic, the reality is we will continue to feel its effects for some time.

With that in mind, this month Psychiatric Times™ shares valuable clinical pearls to support you and your patients. For instance, Teodilo Matos Santana, MD, and colleagues found the pandemic has led to a new variety of malingering. They draw from their clinical experience to shine a light on unique behavioral maladaptations to crises as well as the medical-ethical dilemmas that arise from such. Their clinical pearls are great reminders of the importance of listening to patients and really understanding their circumstances.

Meanwhile, the usual clinical challenges still arise, like finding the best treatment strategies for patients with schizophrenia. Often, there is a need to switch antipsychotics, and doing so can be complicated. To support you in this endeavor, John J. Miller, MD, shares 10 factors to consider when cross-titrating these medications in this month’s continuing education article. His thoughtful explanations provide a road map to successful outcomes.

Of course, you also will find many of the usual clinical articles, features, and commentaries that have you reading Psychiatric Times™ from cover to cover. As we look to the future, our goal continues to be to support you, our readers, in all things psychiatry related.
FROM THE EDITOR

Neuroplasticity and Smart Phones
John J. Miller, MD | Editor in Chief

One of my favorite quotes from philosopher Jiddu Krishnamurti is, “Consciousness is its content.” It makes perfect sense. After reading a book, watching a movie, traveling to Italy, visiting with family over the holidays, finishing a grueling day at work, or surviving a traumatic experience, our mind retains the memories of these experiences in varying regions of our brain. If we ensure a good night’s sleep, the memories of the previous day will be stored for long-term recall in various brain structures during the night by our hippocampus, along with neuronal connections that will allow us to reconstruct all these memory fragments to recreate the experience.

Associative Memories
Most of us have experienced recalling a memory that, in retrospect, was connected to a sensation in the present that is associated with an experience from the past. Whenever I smell pine needles, for instance, I think of my grandmother. She spent her final years in a boarding house called the GreyCroft Inn in Beverly, Massachusetts. My grandmother had an ornamental plant in her room from the White Mountains in New Hampshire that was full of pine needles, and the odor of pine filled her room. Throughout life, when I smell the scent of pine, a memory of my visiting her in her room as a child flashes through my mind.

When memories are stored for the long term, they are broken down into segments that are then encoded in brain regions specific to those segments. Hence, visual memories are stored in the visual cortex, smells in the olfactory cortex, and emotions in the amygdala. At some future time when a segment is activated, like the smell of pine needles in my grandmother’s room, an associated segment from the past that is connected to the segment in the present can appear. This is an efficient way to store complex memories, which can lead to an associative memory surfaceing in the present with just the right cue.

Periodic Prolific Synaptogenesis
In medical school, I was taught that the brain is hardwired at birth. During the past 30 years, neuroscience has definitively shown that this is not the case at all. As our understanding of brain development advanced, it became clear that, during the first 3 years of life, neurons in the brain prolif erately form synaptic connections to be prepared for many of which it will never encounter. From aged 3 years onward, the circuits frequently used strengthen their connections while those serving no function are pruned away. Hence the common phrase, “Neurons that fire together, wire together.”1

We have learned that the brain, with limited space to occupy due to the confines of our skull, maximizes the use of any and all neuronal real estate. True to this quest, the brain’s neuronal connectivity during the first few years of life retains significant plasticity. One well-established example of this is the discovery that in individuals who are born blind and become proficient in reading braille, there are 2 brain-wiring changes that occur with just the right cue.

the ages of 20 and 25 years that the early 20s. It is somewhere between 10 and 12 years and again in the opportunities to rewire the brain to maximize functioning of actively used circuits occurs between the ages of 1 and 3 years, aged 10 to 12 years, and in our early 20s. Each of these periods allows a window of opportunity for the brain to significantly strengthen synaptogenesis for functions that are actively used and to prune away synapses that have been minimally utilized. Additionally, the brain remains plastic throughout our lives, and any new behavior, especially with repetition, will induce synaptogenesis to strengthen the associated neuronal connections. This is nicely demonstrated by the phantom-limb case, as well as by a large body of literature establishing that aggressive occupational and physical therapy after a cerebrovascular accident, which includes restraint of the unaffected limb (constraint-induced movement therapy), can result in a significant improvement in functions that had been lost.5,6

10,000-Hour Rule

In Malcolm Gladwell’s national best-seller Outliers,7 he articulates a common theme in individuals or groups (including Bill Gates and the Beatles) who excel in a particular skill. Simply put, their ultimate accomplishments were preceded by 10,000 hours of learning and practicing that skill. If we spend 40 hours a week engaged in a particular skill for 50 weeks per year, that adds up to 2000 hours per year. After 5 years, we will have accrued 10,000 hours of experience and likely have developed a significant amount of expertise. From a neuroscience perspective, our brain spent 10,000 hours reenforcing and strengthening synapses that are involved in the development and execution of the circuitry that is the foundation of this expertise.

Concluding Thoughts

What does all this have to do with smart phones? As with any tool, behavior, activity, or technology, smart phones have the potential to be either a useful and highly constructive asset or a destructive and harmful diversion from life. After accruing 10,000 hours on a smartphone, our brain has certainly been impacted and rewired in a significant way. An unanswered question that causes me a great deal of curiosity and concern is: What is the impact on brain development during the first 25 years of life when a significant part of each day is spent looking into a smartphone and the resulting cognitive and emotional experiences? Just wondering…

REFERENCES

Psychedelics and the Future of Psychiatry

Once dismissed as dangerous and having little therapeutic potential, psychedelic drugs are gaining mainstream acceptance. Research data continue to demonstrate that, on the whole, these medicines are not only safe, but mostly well tolerated. Although more research is needed to better understand safety, especially in the context of at-risk conditions, these favorable safety profiles are enabling deeper exploration of these medicines.

The term psychedelic was coined in the 1950s by psychiatrist Humphry Osmond, MD, and it literally means “mind-manifesting.” This class of drugs produces changes in perception, thought, and mood with minimal disorientation or confusion. Unlike alcohol, benzodiazepines, and barbiturates, psychedelics do not lead to a slowing of cognitive processes or an acceleration of cognition as seen with stimulants.

Several US states and cities are in the process of legalizing or decriminalizing psychedelics like psilocybin, 3,4-methylenedioxymethamphetamine (MDMA), lysergic acid diethylamide (LSD), and others for therapeutic or recreational purposes. In 2020, the Oregon Ballot Measure 109 was passed, allowing licensed service providers to administer psilocybin products to individuals 21 years and older and making Oregon the first state to legalize psilocybin. The drug will not be available commercially or for home-based use, as strict regulations are in place to ensure psilocybin will be used only under the supervision of trained facilitators. This was a major milestone in psychedelic medicine, as it opened the door for more widespread access to psilocybin therapy in a safe and legal manner.

The US Food and Drug Administration (FDA) has also shown interest in prioritizing the approval of certain psychedelic drugs. Both psilocybin-assisted psychotherapy for major depressive disorder (MDD) and treatment-resistant depression, as well as MDMA-assisted psychotherapy for posttraumatic stress disorder (PTSD), have received the breakthrough therapy designation from the FDA to fast-track the approval process because of the growing clinical evidence demonstrating substantial improvement over currently available therapies.

**Safety Issues and Scaling Up**

The growing research results continue to confirm that psychedelic medicines are not only safe, but well tolerated by the majority of recipients. A psilocybin study found that cases of mental health complications following a psychedelic are rare (<0.1%) even in vulnerable populations (<0.2%), and rarer still with proper screening. Another study examined the classical psychedelics, LSD, psilocybin, and mescaline. It found no evidence of increased rates of mental health problems; in fact, it demonstrated psychedelic use was associated with reduced psychological distress and suicidality. Additionally, results of studies examining psychedelic substance use patterns in humans as well as self-administration in animals suggest that classic psychedelics possess little or no abuse liability and may even be antiaddictive.

Results of other studies suggest psychedelics may have protective effects when it comes to mental illness in general. Pooling more than 190,000 adults, researchers evaluated the relationship of classic psychedelic use and psychological distress and suicidality. They found that lifetime psychedelic use was associated with significantly reduced odds of past-month psychological distress, past-year suicidal thinking, past-year suicidal planning, and past-year suicide attempt. This offers new insight into the potential promise of psychedelics in helping to prevent suicide.

More research is still needed to fully understand safety, especially in the context of at-risk conditions and mechanisms of action. However, the favorable safety profiles are opening doors for deeper exploration of these medicines.

**MDMA**

MDMA-assisted psychotherapy, the psychedelic treatment closest to receiving FDA approval, is currently undergoing phase 3 clinical trials in patients with PTSD. The study included 90 patients with severe, chronic PTSD from a variety of different causes (e.g., abuse, combat, sexual trauma). It is worth mentioning that this was a treatment-resistant group, meaning patients had suffered with PTSD for an average of 14 years without relief. All participants completed a 12-week treatment program composed of 3 full-day sessions, during which they received either MDMA or a placebo, plus weekly nondrug psychotherapy sessions. No serious adverse effects were detected beyond transient, mild symptoms during drug treatment such as nausea or sweating. No increases in suicide risk or potential for abuse were noted in the MDMA group relative to placebo. Two months after treatment, 67% of the MDMA cohort no longer qualified for PTSD diagnosis, compared with 32% of the placebo group. In addition, 88% of those in the MDMA group experienced a clinically significant reduction in symptoms (Figure 1). MDMA is unique in its ability to promote acceptance of and empathy for self and others. In addition to elevating oxytocin levels, MDMA stimulates the release of the monoamines serotonin, norepinephrine, and dopamine, resulting in improved mood and increased sociability. Brain imaging after administration of MDMA shows there is decreased amygdala activation and reduced fear response, allowing the patient to emotionally engage in therapy without becoming overwhelmed by anxiety or difficult emotions. The combination of medication plus psychotherapy represents a new frontier for the FDA, with unique challenges to be addressed such as therapeutic approaches and therapist training.
Psilocybin

Psilocybin, the main psychoactive component of “magic mushrooms,” is currently in phase 2 clinical trials for MDD. As a classic psychedelic, it is an agonist of serotonergic 5-HT$_{2A}$ receptors in the brain, which are particularly abundant in the cortex and regions associated with cognitive functions and social interactions. Stimulation of this receptor has been directly linked to cognitive flexibility, enhanced imagination, and creative thinking.13

In pivotal study results, 71% of individuals with MDD who received 2 doses of psilocybin were treatment responders, and half of the participants entered remission (Figure 2). Some follow-up studies after therapy, although small, have shown lasting benefits.6,14

Concluding Thoughts

Psychedelic medicine is forging ahead as a promising new treatment paradigm, in which psychedelics, paired with psychotherapy, have the potential to treat various mental health conditions. Preliminary findings show successful results for these treatments, with significant clinical improvements and few—if any—serious adverse effects. The emerging results likely have implications for future psychiatric research, education, and policy—and most importantly, they are poised to offer new therapeutic options and improve the lives of those we serve.

Dr Robison is chief medical officer of Novamind; medical director for the Center for Change; and coordinating investigator for the Multidisciplinary Association for Psychedelic Studies’ phase 2 clinical trial examining MDMA-assisted psychotherapy for the treatment of eating disorders.

REFERENCES

COVID-19 Vaccine Mandate
Exemption Requests for Anxiety

Continued from Cover

public health, promote workplace safety, and minimize risk of harm to vulnerable patients. The exemptions, in turn, are important to protect the ability of workers to carry out their chosen occupation without being disqualified by their health status, a widely recognized ethical value. Granting or denying an exemption thus warrants a heavy burden of justification. That difficult standard can be met in some cases, such as exemptions for risk of allergic reaction to the COVID-19 vaccine. Given that serious allergies to COVID-19 vaccines are relatively rare, the degree to which potential exemptions for this reason undercut public health is minimal, particularly under conditions of staffing shortages in which retaining the services of health care workers with serious allergies is itself an important goal. Furthermore, risk to workplace safety can be mitigated through regular testing, masking, and social distancing.

Given the rapid implementation of COVID-19 vaccine mandates, there has been limited time for professional societies to develop guidelines for how such requests should be handled, leaving organizations to independently navigate this space. To evaluate and determine dispositions for COVID-19 vaccine exemption requests, many health care organizations have formed committees consisting of representatives from human resources, legal affairs, ethics, and relevant medical specialties. This has been the case for one academic medical institution, whose committee received several exemption requests citing anxiety about the COVID-19 vaccine. A workflow had been developed for other medical conditions, such as allergic reactions, as well as for religious concerns; however, psychiatric exemption requests had not been anticipated and, thus, no workflow had been established.

The committee reached out to the institution’s BH leadership for consultation on handling these anxiety-related exemption requests. The BH leaders convened a team consisting of psychiatrists, a psychologist, and a psychiatric nurse practitioner. The team felt it was crucial to seek guidance from professional societies and experts in anxiety disorders. At the time, none of the professional or health care organizations contacted had developed a policy for such exemptions.

Initially, the BH team considered if exemption requests for anxiety should mirror requests based on other medical conditions. Employees requesting exemptions due to allergies, for example, are given a short (no longer than 6-month) extension of the vaccination deadline and the opportunity for evaluation and treatment at the medical center’s allergy clinic at no cost, or with a different allergist of the employee’s choosing at their own expense. A list of possible outcomes from such requests is available in the Table.

In all cases, the allergist—with the consent of the employee to release the information for purposes of processing the exemption request—makes a recommendation to the vaccine committee. The BH team felt that several questions needed to be answered to determine if the allergy model was appropriate for anxiety.

Is Anxiety a Legitimate Reason Not to Be Vaccinated?

A foundational principle in the treatment of anxiety disorders is that one must overcome avoidance and directly confront the source of anxiety to fully recover. This taps into the folk wisdom of “facing your fears,” and it is backed by decades of psychological research and clinical neuroscience. Exposure therapy, a cornerstone of cognitive behavioral therapy (CBT) for anxiety, aims to help individuals conquer their anxiety by repeatedly and strategically exposing them to personalized fear-inducing cues or scenarios. The underlying mechanism most likely relates to formation of an inhibitory pathway to calm the amygdala, which generates the fear response; the process is called fear extinction.

The efficacy of exposure entails a lesson in what not to do for someone with an anxiety disorder—which is to facilitate an avoidance strategy as part of their management of anxiety. Accommodating someone’s fear will perpetuate it by preventing both the opportunity for learning and the creation of inhibitory pathways. It is therefore antithetical for clinicians specializing in the treatment of anxiety disorders to consider anxiety as a reason for exemption. This would, in effect, endorse avoidance of something—in this case, a vaccine—that is widely considered to be safe for individuals without medical contraindications.

It is noteworthy that the management of both allergies and anxiety involves exposure to the offending stimulus in order to achieve desensitization. The difference is that allergies may actually be life-threatening, whereas anxiety—although it may result in fears of harm or even death—is not. In fact, and in contrast, anxiety is most harmful when exposure to the source of the anxiety does not occur. Hence, vaccine anxiety is very unlike a vaccine allergy. The allergy policy previously outlined balances the important benefits of vaccine mandates against the therapeutically appropriate handling of individual employees’ allergies. But in this case, it is difficult to see how one can justify risking the important benefits of vaccine mandates by offering permanent exemptions for vaccine-related anxiety, given that the avoidance behavior being facilitated would, if anything, be more likely to exacerbate than to ameliorate the underlying problem. Taken on its own, facilitating problematic health behaviors is an inadequate reason to forgo the important benefits of a mandate.

What Are Some Strategies for Handling Such Exemption Requests?

Ultimately, the team concluded that anxiety was not a reason for granting permanent exemptions. To take this stance is not to say that anxiety should not be handled as seriously or compassionately as any other request for a medical exemption. It does not work to say “just get over it” to someone whose innate (ie, subcortical, nonconscious) survival mechanisms are sounding an alarm, any more than it works to tell someone with an essential tremor to “just hold still.” Although we may not be able to approve a vaccine exemption request for the reason of anxiety, we can and must still consider a reasonable medical accommodation.

The response that this group recommends is to allow a standardized delay in the deadline for vaccination that would enable the employee with anxiety to receive treatment from a resource of their choice, such as an employee assistance program or a psychologist and/or therapist who specializes in anxiety disorders. The goal would be to help the employee to get vaccinated by the end of treatment, if that is the individual’s ultimate goal as well. The average number of sessions of CBT for anxiety is 8 to 12, which, with weekly meetings, would mean 2 to 3 months of treatment. There is some evidence that

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<th>Table: Possible Outcomes of Requests Made by Employees for Exceptions From Vaccine Requirements Due to Allergies</th>
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<tr>
<td>The employee receives the vaccination at the allergist’s office.</td>
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<td>The allergist recommends an additional extension at the end of the initial delay.</td>
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<tr>
<td>The allergist recommends a permanent exemption.</td>
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<td>The allergist determines there is no valid concern.</td>
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more sessions may lead to further improvements in anxiety, but 3 months could strike a balance between the time-sensitive need for immunity and allowing adequate time for therapy with a clear and specific goal. Similarly, a medication response can be expected within about 3 months.

At the end of the prespecified delay, the employee will have to decide to be vaccinated or not. This solution takes employees’ concerns seriously and affords time to treat anxiety that may make vaccination difficult. It also avoids disincentivizing the employee to work on their anxiety because the extension period is limited.

Should We Be Concerned About Claims Made in Bad Faith or Abuse of This System?

We can never know someone’s true motivations, and in this case, there are 2 individuals whose intentions are relevant: (1) the employee submitting the vaccine exemption request and (2) the medical provider signing it. Unfortunately, we can assume that there will be individuals who will seek a loophole to circumvent this new requirement, and anxiety might be easier to malinger than an allergy, given the lack of measurable biomarkers. There will also be those who do not have an anxiety disorder as defined by the DSM-5, but instead are suffering from distress related to the mandate itself. The very need for the mandate comes at least in part from the fact that the COVID-19 vaccine rollout has been fraught with political polarization, ideological flame-fanning, and outright misinformation. To the average person caught in this maelstrom, making a decision may feel nearly impossible, with the stakes being one’s employment and livelihood. The medical provider signing the exemption is also not excluded from misunderstanding or conflicted interests, including wanting to support the patient making the request.

By excluding anxiety as a reason for exemption, claims made in bad faith can be minimized. Based on our experience, most physicians have not been signing exemption requests for reasons related to mental health. It would be reasonable for organizations to initially grant a 3-month delay as previously described. Organizations could then monitor outcomes and sequelae, such as the success of this accommodation in maintenance of employment and the number of exemption requests for anxiety over time (eg, determining whether requests increase if word spreads among individuals seeking a delay for any reason). If organizations detect an increase in requests among the employed population, one strategy might be reaching out to the signing medical provider for additional information prior to granting the accommodation. We would also recommend keeping this policy confidential so that it will not be readily utilized by those looking to delay vaccination.

Do Behavioral Health Conditions Constitute a Valid Reason for Exemption?

One of the challenges of this question is the lack of precedent. To the knowledge of these authors, there is no reason to believe that any behavioral health condition would constitute a valid reason for exemption. On October 1, 2021, the ethics committee of the American Psychiatric Association (APA) made a public statement, which is excerpted here:

Psychiatrists should not provide vaccine exemptions for those with anxiety or other mental health symptoms, nor should institutions accept such exemptions written by nonsympathetic physicians, absent compelling evidence that the individual’s mental health condition is so extreme that it rises to the level of a medical reason which prevents the individual from receiving vaccination. The individual preference or request of a patient cannot justify departure from a psychiatrist’s public health responsibilities to support vaccine mandates. Instead, any patient with anxiety or other mental health symptoms related to vaccination should be offered support and treatment as needed to enable them to receive vaccination.

Concluding Thoughts

We recommend that interested individuals and organizations review the APA’s opinion in its entirety and look for updates. It is critical to have an ongoing conversation about the humanitarian, scientific, public health, and ethical factors involved in a new medical mandate. Like the scientific method or any good dialectic, this conversation about ethics and strategy is just a start and may evolve substantially over time.

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Dress Rehearsal

Richard Berlin, MD

– for my Boston Symphony Orchestra neighbors

Gone for the pandemic year, they’ve returned like songbirds, exhausted from flight but wild to swagger the songs they carry. A month deep into their embouchure rehab, I hear them rehearse as I dance down their dirt road, First Trombone nailing a tune that brings down the house, Second Trombone matching him note for note, amping up the tempo, playing scat singer loose, Oboe at the third driveway trilling call and response with a wood thrush, both lost in their Birdland jazz, Tuba on his deck blasting oom-pahs strong enough to loosen nails, and Horn on the hilltop calling the gods to join their dirt road symphony, wind brushed leaves applauding this July 5th morning before opening night.

Embouchure is the use of the lips, facial muscles, tongue, and teeth in playing a wind instrument. This includes shaping the lips to the mouthpiece. The word is of French origin from the root “bouche” meaning “mouth.”

Dr Berlin has been writing a poem about his experience of being a doctor every month for the past 24 years in Psychiatric Times™ in a column called “Poetry of the Times.” He is instructor in psychiatry, University of Massachusetts Medical School, Worcester, Massachusetts.
Comorbidity: The concept is simple enough, but in practice, comorbidity drives complexity and presents the specters of diagnostic ambiguity and therapeutic unpredictability.1 The psychiatric community maintains a healthy fascination with symptom associations and relationships between diseases and conditions, both medical and psychiatric. In many ways, attention to these relationships and understanding how they affect disease trajectory and therapeutic effectiveness, for example, get to the heart of psychiatry and the human need to interpret reality for ourselves and others.

Reality must be described before it can be interpreted. Philosophical and medical efforts from the phenomenology of Karl Jaspers, MD, and Edmund Husserl, PhD, and the descriptive psychopathology of the DSM display the long-standing imperative to accurately describe and understand reality for patients, caregivers, and other clinicians.2 The comingling of comorbidities provides an enriching, descriptive sketch that should balance clinicians’ understanding of patients’ symptoms, conditions, vulnerabilities, and protective factors.

Mimesis: imition, representation, expression, the act of resembling. Getting reality right has been the domain of not only a good psychiatric interview but art and literature since antiquity.3 Mimesis refers to the depiction of nature—itself to influencing the characterizations of patients’ reality, conditions, and life trajectories. Comorbidity indices such as the Charlson Comorbidity Index or Kaplan-Feinstein index provide the clinician with a global impression of impairment, or inversely, functionality. But numerical scales do not provide the same texture or feeling of what the patient experiences. The interplay of signs and symptoms, along with a patient’s reflections and interpretations of their realities, provides a palette from which the psychiatrist forms a visual representation of the patient’s world. This representation is mimesis and forms the basis from which interpretations arise and discussions can be productive and therapeutic. There is an aesthetic to mimicry that is seen through exemplary psychiatry. Understanding comorbidity is integral to this action and the practice of psychiatry.

Dr McFarland is an oncologist who also works in the field of consult-liaison psychiatry at Northwell Health/Lenox Hill Hospital, in New York, NY. Dr Grassi is professor and chair of Psychiatry, University of Ferrara, Department of Biomedical and Specialty Surgical Sciences, and director, University Hospital Psychiatry Unit, S. Anna University Hospital and Health Authorities Ferrara, Italy. Dr Riba is professor, Department of Psychiatry, and director, PsychOncology, University of Michigan Rogel Cancer Center, Ann Arbor, MI; she also is former Deputy Editor in Chief Emeritus of Psychiatric Times. They report no conflicts of interest concerning the subject matter of this Special Report.

REFERENCES
New Directions for Insomnia and Bipolar Disorder

Chris Aiken, MD

The average patient with bipolar disorder (BD) spends half their life struggling with mood symptoms and the other half struggling with sleep.1,2 Insomnia persists in 70% of patients even when their mood is stable, and these sleep problems put them at risk for more episodes of mania and depression (Table 1). Some clinicians are liberal with hypnotics, while others prefer the lower abuse potential of sedating antidepressants like trazodone. Both these approaches have problems. Fortunately, there are also new therapies that improve mood and sleep by entraining the circadian rhythm (Table 2).

Benzodiazepines and Z-Hypnotics

It seems intuitive that a benzodiazepine or z-hypnotic (eg, eszopiclone, zaleplon, zolpidem) can halt the progression of insomnia into mania, but the idea has never been adequately tested. These GABAergic hypnotics lack controlled trials in BD, and the few observational studies paint a mixed picture.

A chart review of 278 z-hypnotic trials in adolescents with BD concluded that the drugs improved sleep in 40% to 60% of patients and did not lead to abuse with long-term use.3 On the other hand, reports document 30 cases of high doses of zolpidem and regular doses of alprazolam and triazolam inducing mania.4,5

In contrast, clonazepam and lorazepam appear safer, with small controlled trials suggesting that these agents do not worsen, and may improve, manic symptoms (the benzodiazepines were not used as hypnotics in these trials).6 However, over the long term, benzodiazepines carry risks of tolerance and dependence, and long-term use may worsen cognition and mood in BD, according to nonrandomized studies that attempted to control for the confounding tendency to prescribe benzodiazepines in more severe cases.7,8

Sedating Mood Medications

Another approach to insomnia in BD is to choose mood stabilizers with sedative effects. Many antipsychotics are sedating, but some have more meaningful benefits in sleep quality; these include quetiapine in particular, and possibly lamotrigine, olanzapine, risperidone, and ziprasidone.9 Lithium is rarely sedating, but it does have positive effects on the circadian system, such as dampening the phase-advance (“night owl”) tendency that is associated with poorer health and greater risk of depression.10

Sedating antidepressants are more problematic, particularly in bipolar disorder, in which the risk of manic induction is high. Most, including trazodone and mirtazapine, are associated with case reports of triggering mania. In a retrospective study, patients with BD who used sedating antidepressants for sleep were significantly more likely to develop mania and episode acceleration than those who took traditional hypnotics.11

Melatonin Agonists

Melatonin agonists have captured the interest of investigators because of their potential to realign the circadian system, which is often disrupted in BD. Pure melatonin failed to improve sleep, mania, or rapid cycling in 2 small controlled trials,12 but the melatonin agonist ramelteon has intriguing results from 3 industry-sponsored, randomized, placebo-controlled trials in BD. Although ramelteon failed to improve sleep or mania, it did prevent depression in patients who struggled with insomnia.

The first study tested ramelteon in 21 patients with acute mania and found a reduction in depressive symptoms but no benefit in mania or sleep.13 Next, ramelteon was tested in 83 patients with BD who had active insomnia but stable mood. For 6 months, they took either placebo or a nightly dose of ramelteon 8 mg. As in the first trial, ramelteon did little to improve sleep (there was only a nonsignificant trend), but it did lower the risk of depression, more than doubling the time to a new episode from 84 to 188 days (P = .02).14 A larger study attempted to replicate that finding, but the results were negative across all outcomes.15

One explanation for these intriguing results is that the positive trials enrolled patients with active insomnia, while the negative trial did not, suggesting that ramelteon might have preferential effects in patients with disturbed circadian rhythms. But then why didn’t the drug improve their sleep? These studies relied on subjective measures of sleep, and ramelteon has a poor track record on subjective outcomes. In primary insomnia, it improved subjective sleep onset by only 4 minutes over placebo and objective sleep onset by 9 minutes. Benzodiazepines showed the reverse pattern, improving subjective onset by 14 minutes but objective onset by only 4 minutes (placebo, by the way, is no dud, and improved sleep onset by 8 to 20 minutes).16

One thing to take away from this is the importance of setting realistic expectations when starting patients on ramelteon. This hypnotic is not like the others; it is relatively nonsedating and has no anxiolytic, amnestic, or rewarding effects. On the one hand, those qualities improve on its safety, but they are unlikely to endear it to patients with BD, who often want a hypnotic to quiet the anxious, racing thoughts that rev up as they try to fall asleep. Ramelteon will do none of that, but nor will it cause patients to fall, overuse their medication, or engage in complex sleep behaviors like cooking or driving in the middle of the night. One positive aspect that most patients appreciate is the lack of tolerance and withdrawal with ramelteon. Rather than wearing off, ramelteon’s sleep benefits built up over weeks to months in some studies.17

Dark Therapy

While ramelteon is a melatonin agonist, dark therapy is a behavioral treatment that enhances endogenous melatonin by keeping patients in a pitch-dark room overnight. Dark therapy was developed by Thomas Wehr, MD, who speculated that evening darkness might improve sleep and mania in the same way that morning light improves depression and circadian rhythms. In the 1990s, he recruited normal participants with mild sleep problems to the National Institute of Mental Health, where they stayed in a pitch-dark room overnight from 6:00 pm to 8:00 am. After a few weeks of this dark therapy, their sleep improved.18 Next, he turned his attention to BD, and found that the same protocol stabilized refractory rapid cycling.19

Further studies supported Wehr’s observation, but it was not until the discovery of blue light–blocking glasses that dark therapy became practical for everyday use. In theory, the physiologic changes associated with total darkness might be achieved by blocking blue light, because the receptor that regulates melatonin secretion—melanopsin—responds only to the blue spectrum. The hope in that theory is that patients might be able to practice dark therapy while still being able to see in the evening.

Psychiatrist James Phelps, MD, first tested that hope in private practice, and his results were later confirmed in a randomized, placebo-controlled trial in Norway. For the entire evening from 6:00 pm to 8:00 am, patients hospitalized with acute mania wore blue light–blocking glasses or, if sleeping or trying to sleep, stayed in a pitch-dark room without the glasses. Within a week, their mania improved with a large effect size (1.86) compared with a placebo group that wore gray glasses.20

The dark therapy protocol can be gradually relaxed after recovery, allowing patients to put the glasses on a few hours before bed to prevent future episodes. That relaxed protocol also improves the sleep, according to 3 randomized controlled trials.
in primary insomnia. Wearing blue light–blockers 1.5 to 3 hours before bed helped patients fall asleep earlier and stay asleep longer, and improved sleep quality as well as mood and cognition on the following days.19-24 However, blue light blockers do not have a strong sedative effect. In line with their circadian mechanism, they improve the regularity of sleep more than they improve subjective measures of insomnia.23

A critical step in deep therapy is finding glasses that filter close to 100% of blue light. Lenses that were tested in clinical trials include Uvex Skyper S1933X, Uvex Ultra-spec 2000 ($10 to $15) and, for more comfort at a higher price, glasses at lowbluelights.com ($50). More information on the nuts and bolts of deep therapy is available in the Psych Pearls podcast from August and October 2021.25

**CBT-Insomnia**

Cognitive behavioral therapy for insomnia (CBT-i) is thought to work by stabilizing the circadian system, making it a natural fit for mood disorders. In unipolar depression, CBT-i improves mood and sleep, but the therapy is often avoided in BD because it requires patients to limit their time in bed, raising concerns that this sleep deprivation could triggermania. In 2015, Allison Harvey, PhD, and colleagues at the University of California – Berkeley modified the CBT-i protocol to include a built-in safety valve for BD (CBT-iBD). The newer therapy limits bed restriction to no fewer than 6.5 hours.

CBT-iBD also includes techniques to address common circadian rhythm abnormalities in BD, such as sleep inertia (a prolonged sense of grogginess in the morning) and nocturnal hyperactivity. To counter these sleep-disrupting tendencies, patients develop a wake-up routine encompassing bright light and energizing activity, and an evening wind-down routine in which the lights are dimmed and screen time ceases.

To test the therapy, Harvey recruited 58 patients with stable BD and active insomnia and randomized them to CBT-iBD or a psychoeducational therapy. At the end of the 8-week therapy, patients in the CBT-iBD group were sleeping better compared with controls, but more profound changes came later. After 6 months, those who learned CBT-iBD had an 8-fold reduction in mood problems, spending an average of 3.3 days in a mood episode vs 25.5 days for controls.3

Later, Bryony Sheaves, DClinPsy, BSc, CPsychol, and colleagues adapted CBT-iBD for patients with schizophrenia, major depression, and BD in an inpatient crisis unit. The 2-week program improved sleep and well-being, and it hastened discharge by 8.5 days compared to treatment as usual.36

It can be difficult to find therapists who practice CBT-insomnia, but the core program is available through a prescription app (Sonryst) or a free, VA-sponsored app (CBT-i Coach). These programs can be adjusted for BD with the modifications described above.

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**The Young and Old**

Dark therapy and CBT-i are safe in the young and old, and a few tips can help adapt these therapies for different ages. Adolescents often have severe night-owl tendencies, which can be corrected by having the patient wake up 15 to 30 minutes earlier each day and wearing blue light–blockers in the early evening (e.g., 5:00 pm to 8:00 pm). Napping is common in older adults but is discouraged in the CBT-i protocol. One compromise is to have the patient eliminate naps during the therapy, and then gradually add them back in once regular sleep is restored. Then they can continue the naps as long as they do not cause a relapse into insomnia. Finally, for patients of all ages who are afraid of the dark, there are nightlights that emit zero blue light (at lowbluelights.com and Amazon).

Although no hypnotics are FDA approved in children and adolescents, lithium and several antipsychotics (eg, quetiapine) are approved for them. In the elderly, the risks of falls and cognitive impairment have placed most hypnotics on the “inappropriate” list of the Beers criteria, although melatonin is well studied in older adults and approved by the Beers.17

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**The Bottom Line**

Treating insomnia in BD is both an art and a science, requiring practitioners to balance the patient’s goal of rapid sedation with the more therapeutic approach of retraining the circadian rhythm. Circadian therapies like ramelteon, dark therapy, and CBT-insomnia have a slow build, but they promise more lasting and substantial benefits for mood and sleep than fast-acting hypnotics.

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### Table 2. Potential Treatments

<table>
<thead>
<tr>
<th>Type</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z-hypnotics or benzodiazepines</td>
<td>Eszopiclone, zalepon, zolpidem; lorazepam, temazepam component 4</td>
</tr>
<tr>
<td>Antipsychotics with sleep benefits</td>
<td>Quetiapine; possibly lamotrigine, olanzapine, risperidone, ziprasidone</td>
</tr>
<tr>
<td>Mood stabilizers with circadian benefits</td>
<td>Lithium</td>
</tr>
<tr>
<td>Melatonin agonists</td>
<td>Ramelteon</td>
</tr>
<tr>
<td>Environmental/physical modalities</td>
<td>Dark therapy; blue light–blocking glasses</td>
</tr>
<tr>
<td>Psychotherapy</td>
<td>Cognitive behavioral therapy for insomnia</td>
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### References

Helping Patients With Attentional Difficulties and Maladaptive Use of Psychoactive Substances

Steve Adelman, MD

The assessment and treatment of patients with comorbid attention-deficit/hyperactivity disorder (ADHD) and substance use disorder (SUD) can be straightforward, except when it is not. The real world of clinical practice is often not as cut-and-dry as the controlled world of clinical research that typically informs our decision-making processes. When does it make sense to prescribe an abusable medication to a patient who may also suffer from SUD? What clinical circumstances dictate prudence and, perhaps, limit-setting? In this case-based review, I will utilize a series of fictionalized clinical anecdotes to help psychopharmacologists determine how to approach prescribing stimulants to patients who may or may not be using psychoactive substances such as cannabis, alcohol, and cocaine.

ADHD in school-age children is known to be a risk factor for the subsequent emergence of SUDs in young adults, especially when the ADHD has not been effectively treated. Armed with knowledge that untreated ADHD affects children adversely, many pediatricians and child psychiatrists routinely prescribe stimulant medications for children diagnosed with ADHD—to an extent that now suggests the possibility that this condition is sometimes being overdiagnosed and, consequently, overtreated. In the following case, trusting parents and clinicians did not detect an emerging SUD in a high school freshman.

**ANECDOTE 1**

A well-spoken boy, aged 14 years, from a “good” family was referred to a child psychiatrist by his pediatrician after failing to respond to methylphenidate extended-release (ER) for “mild ADHD.” The child psychiatrist reviewed the electronic health record, where the social history indicated “no concerns about alcohol, pot, other drugs.” The boy’s history revealed declining school performance throughout eighth grade, and he appeared distracted and unkempt during the interview. Over the next several months, increasing doses of immediate-release (IR) amphetamine/dextroamphetamine were prescribed with an equivocal response. The patient’s mother called for an early refill, stating that her son’s gym locker had been broken into. The psychiatrist met with the patient and obtained a urine drug screen, which came back with a THC level of 584 ng/mL. When confronted, the young man broke down, begged the psychiatrist not to tell his parents, and admitted that he was selling some of his stimulants to pay for weed, and that he himself had crushed and snorted his amphetamine pills on at least a few occasions.

**DISCUSSION OF ANECDOTE 1**

This situation is concordant with my experience in a variety of ambulatory psychiatric settings. In many real-world outpatient psychiatric settings, empirical stimulant trials to treat presumed ADHD are often undertaken, and urine drug screening may be underutilized at the outset of treatment, especially for younger patients. It may appear to the addiction psychiatrist that some patient-centered clinicians possess an alarmingly low index of suspicion that SUD either may be contributing to attentional difficulties or is perhaps the primary problem. Unfortunately, many child psychiatrists receive little to no training in child and adolescent addiction psychiatry, despite the fact that there may be much merit in conceptualizing addiction as a pediatric disease. Although clear-cut ADHD in a younger child may presage the emergence of SUD in teenagers and young adults, patients like this 14-year-old may appear, at first glance, to be more straightforward than they are. This boy’s primary diagnosis may be SUD, not ADHD.

Psychopharmacologists treating adult patients should routinely endeavor to enrich the fact pattern when they are called upon to prescribe controlled substances for individuals who carry a history of ADHD. Additional assessment strategies come to mind when considering Anecdote 2.

**ANECDOTE 2**

A new male clinic patient, aged 25 years, tells his psychiatrist that he suffers from ADHD. He shows the psychiatrist a prescription bottle of prescribed stimulants (IR amphetamine/dextroamphetamine) with 3 pills left. His previous psychiatrist is known to have retired from practice a few months back. The stimulant dose is average, and he assures his new psychiatrist that he takes his medication by mouth, as prescribed. He has a negative medical history, and other than ADHD diagnosed in elementary school, he has no known psychiatric history. When asked about alcohol consumption, he acknowledged drinking “a beer or two” on weekends, but he otherwise denies substance use. He is the father of an infant who is napping in a stroller in the waiting area, tended to by the patient’s girlfriend. The patient works as a manager in a call center, and he attributes his promotion to the medication’s efficacy.

This situation is concordant with my experience in treating adult patients with ADHD who may or may not be using psychoactive substances. This patient appeared straightforward, did not reveal his history of binge drinking to his new psychiatrist, and minimized his use of alcohol and drugs when interviewed by physicians, who often move forward quickly in taking the substance use history at face value without seeking details beyond the superficial information provided by the patient. In the case described, a recent binge, combined with a proconvulsant medication, had a serious and potentially catastrophic impact on the patient.

To what extent should the prescribing physician or clinician dig deep in such cases? One can readily speculate, in retrospect, about the measures the new psychiatrist might have taken. Records from the previous psychiatrist might have been obtained. Reviewing primary care records or speaking with the primary care provider often adds helpful data. In this case, information from the patient’s significant other could have been incorporated into the initial interview—she was right there in the waiting room and could have been artfully engaged in the initial evaluation session. When it comes to ruling out a current SUD, more information from multiple data sources is almost always necessary.
Clarifying. This takes time, but it is good medicine—good psychiatry. Because adults with ADHD are 3 times more likely to suffer from an SUD than those without ADHD,3 psychopharmacologists should routinely conduct a thorough substance use history, with multiple data inputs. This is a best practice that helps to protect patients, who may not be disclosing important information to the prescribing clinician.

**ANECDOТЕ 3**

A homeless female veteran, aged 30 years, was incarcerated after her fourth shoplifting arrest. She appeared unwell, with hypertension, tachycardia, diaphoresis, agitation, and confusion. Alcohol-withdrawal delirium was diagnosed, and she responded to benzodiazepines and supportive treatment. A toxic screen was positive for cocaine. During her 3 months of incarceration, she was seen by a mental health counselor with experience in the special education system. The inmate’s mental status and school history were consistent with a diagnosis of adult ADHD. The prison psychiatrist opted not to initiate pharmacotherapy, and the patient was discharged, while remaining on probation, to a halfway house for veterans with co-occurring disorders. An addiction psychiatrist affiliated with the Veterans Health Administration opted to treat her with methylphenidate hydrochloride ER tablets, provided she remained in the halfway house, which has daily 12-Step meetings and a robust urine drug screening program. Frequent drug random drug testing was also a condition of her probation. With 6 months, the veteran was working gainfully and fully engaged in outpatient treatment, and she expressed a strong desire to stay on track and remain a productive member of society.

**Table. Universal Precautions for Psychiatrists (Adapted and Generalized)**

| 1 | Make careful diagnoses, with appropriate differential. |
| 2 | Conduct comprehensive assessment encompassing risk of substance use disorder (SUD); family history of SUDs; patient-centered drug-use assessments and interviews; risk assessment surveys; and utilization of prescription monitoring programs. |
| 3 | Include risks of potentially problematic psychoactive medications in informed consent. |
| 4 | Include abstinence expectations, a standardized approach to emergent drug-seekin behaviors, and routine drug screening in treatment agreements. |
| 5 | Carefully consider nonpharmacological symptom-reduction strategies. |
| 6 | Emphasize and discuss pharmacological alternatives without addiction liability. |
| 7 | Conduct pre- and postintervention assessments of symptoms and level of functioning. |
| 8 | Conduct periodic reviews of relevant co-occurring diagnoses and comorbid conditions, including SUDs. |
| 9 | Develop formal documentation including all of the above information and data. |

**Concluding Thoughts**

The anecdotes that have been presented and discussed demonstrate that when approaching the pharmacotherapy of ADHD in patients who may be misusing psychoactive substances, artful clinical decision-making should be evidence-based and informed by best practices that are routinely utilized by addiction professionals in the assessment and treatment of patients who suffer from SUDs. Because a history of ADHD is a risk factor for SUDs,2 it is clinically prudent to carefully assess all ADHD patients for current substance misuse. Gourlay’s universal precautions for treating pain (and minimizing addiction liability) have been utilized to develop “Universal Precautions for Psychiatrists” for safe, addiction-savvy treatment of anxiety disorders.4 This specific set of universal precautions is further adapted and generalized in the Table.

These universal precautions, initially developed by Gourlay4 to facilitate the addiction-informed treatment of chronic pain and then adapted to promote the addiction-informed treatment of anxiety disorders,5 are now presented in a format that can be utilized whenever a physician or other prescribing professional is considering whether or not to prescribe a potentially abusable psychoactive medication to any patient. Bastiaens et al4 indicate that individuals with ADHD and co-occurring SUDs, with or without antisocial personality disorder, often respond positively to nonstimulant medications that are prescribed for ADHD. Some addiction psychiatrists make it a practice to begin the pharmacotherapy of ADHD with trials of nonaddictive medications. In fact, this practice may be particularly useful when a new patient presents with a sense of urgency in requesting a schedule II stimulant. When the use of stimulants clearly seems indicated, ER formulations and the prodrug lisdexamfetamine6 may be a safer first choice than IR stimulant compounds with greater abuse liability.

In conclusion, ADHD and SUDs are common conditions that frequently co-occur. A carefully conceived and executed integrated treatment plan that pays adequate attention to ADHD symptoms and also to possible psychoactive substance misuse is a universal best practice. When clinicians without addiction expertise notice problematic behaviors that may indicate that there is more going on than initially meets the eye, a subspecialty consultation may be useful in helping the patient while mitigating risk.

**Dr Adelman is a coaching and consulting psychiatrist who is board certified in psychiatry, addiction medicine, and coaching (BCC). He launched www.AdelmanMD.com after 8 years directing Physician Health Services, Inc. He is on the faculty of the University of Massachusetts Medical School as well as a consultant in psychiatry in the Division of Alcohol and Drug Abuse of McLean Hospital, an affiliate of Harvard Medical School.**

**REFERENCES**

SGM College Students

As separate groups, college students with ADHD and college students who identify as a sexuality and gender minority (SGM) have increased risk for functional impairments, psychiatric comorbidities, and risky behaviors. According to Destiny Orantes, PhD, from Syracuse University, and colleagues, previous research had not considered if these outcomes are further increased in SGM students who have ADHD. Orantes shared findings from their recent research in a poster presentation. The study assessed functional impairments, psychiatric comorbidities, and engagement in risky behaviors in 4 groups: (1) SGM students with ADHD, (2) SGM students without ADHD, (3) non- SGM students with ADHD, and (4) non-SGM students without ADHD. Data from the American College Health Association-National College Health Assessment 2019-2021 III were used. The researchers also sought to examine the prevalence of ADHD in SGM college students.

They found ADHD prevalence increased in SGM populations: 15% compared with 8% in non-SGM individuals. Additionally, SGM students with ADHD reported the highest levels of functional impairments, substance use, and psychiatric comorbidities.

The research results suggest, Orantes said, that future studies should consider the underlying reasons for SGM students having high rates of ADHD, and how best to reduce these negative outcomes. Specifically, treatment plans should take into account the separate difficulties students face from their ADHD diagnosis and their SGM identities, as well as how best to target the risky behaviors and comorbidities. —Leah Kuntz

The APSARD Health Equity Task Force

“The [APSARD] task force was launched in relation to the amazing societal changes that are happening...in association with the awareness that equity means creating fair, equitable opportunities for all of us,” Martin Katzman, MD, FRCPC(C), APSARD Health Equity Task Force chair, told attendees. “We’re hoping to build connections within the APSARD community, to enhance diversity of the organization, and to reach out across boundaries as well as to partner within all of our communities to raise awareness and to increase opportunities for treatment for populations that may not get the same access to treatment.”

Amy Glasofer, DPN, RN, nurse scientist with Virtua, shared an analysis of 41 studies relating to ADHD, race, ethnicity, and disparity; Catherine Dingley, PhD, RN, FNP, FAAN, associate professor in the Nursing Department of the University of Las Vegas, Nevada, also worked on the project.

They found 66.7% of studies noted Black children were significantly less likely than white children to be diagnosed with ADHD, and 65% of Black children with ADHD were significantly less likely than white children to receive medication. In addition, compared to white children, she noted Black children were more likely to discontinue medication and more likely to experience gaps in treatment; less likely to receive an agonist alone; and more likely to receive significantly lower doses of stimulant. The findings suggest that, although diagnostic disparities have been reduced over time, treatment disparities still exist for minority children with ADHD. —Erin O’Brien

REFERENCE


PRESCCHOOL-AGED PATIENTS

“ADHD in preschool children is a valid and reliable condition,” reported Ann Childress, MD, president of the Center for Psychiatry and Behavioral Medicine, Inc, in Las Vegas, Nevada.

According to the 2014 National Survey of Diagnosis and Treatment of ADHD and Tourettes, 30% of children diagnosed with ADHD receive their diagnosis before age 6. 16% receive the diagnosis at 4 years or younger. Impairment can be great for these patients, Childress said. For example, an epidemiological review of preschoolers diagnosed with ADHD found more than 40% had been suspended from school or daycare and about 16% had been expelled. In comparison, less than 1% of young children without ADHD were suspended.

The actions of young children with ADHD pose safety risks to themselves due to higher levels of hyperactive impulsivity, she said. These are kids who are running out in traffic. They’re jumping off things and breaking bones. They’re doing things that are dangerous, and they really need treatment for their safety,” she explained.

Childress reviewed efficacy and safety data for a number of common medications, noting some small behavior improvements as a result of the study medications. However, medications were associated with adverse events, including insomnia, gastrointestinal issues, irritability, sedation, and repetitive behaviors and thoughts. She also noted not all of these medications have been approved for the youngest patients.

Fortunately, there is good evidence for the efficacy of nonpharmacological interventions for preschoolers with ADHD, Childress reported. The New Forest Therapy, Helping the Noncompliant Child, and the Incredible Years series were among the programs she noted that have demonstrated efficacy. Furthermore, she spoke highly of parent training models that foster the implementation of positive reinforcement to promote positive behaviors; ignoring low-level provocative behaviors; and responding in a clear, consistent, and safe manner to unacceptable behaviors.

“You have to carefully consider both developmental aspects and comorbidity when you’re establishing a diagnosis, and the medication efficacy and tolerability profile may not look as good in the little guys as it does in older children,” she concluded.—Heidi Anne Duer, MPH

REFERENCES

**INDICATION AND LIMITATIONS OF USE**

Vyvanse is indicated for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in adults and pediatric patients 6 and older. Pediatric patients with ADHD younger than 6 years of age experienced more long-term weight loss than patients 6 years and older. Vyvanse is not indicated or recommended for weight loss. Use of other sympathomimetic drugs for weight loss has been associated with serious cardiovascular adverse events. The safety and effectiveness of Vyvanse for the treatment of obesity have not been established.

**CONTRAINdications**

- Known hypersensitivity to amphetamines or other ingredients of Vyvanse. Anaphylactic reactions, Stevens-Johnson Syndrome, angioedema, and urticaria have occurred.
- Use with monoamine oxidase inhibitors (MAOIs) or within 14 days of stopping MAOIs (including MAOIs such as linezolid or intravenous methylene blue), because of an increased risk of hypertensive crisis.

**Warnings and Precautions**

- Prior to and during treatment assess for the presence of cardiac disease. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmia, coronary artery disease, and other serious heart problems. Sudden death, stroke and myocardial infarction have been reported in adults with CNS stimulants at recommended doses, as well as sudden death in pediatric patients with structural cardiac abnormalities and other serious heart problems while taking CNS stimulants at recommended doses. Further evaluate patients who develop exertional chest pain, unexplained syncope, or arrhythmias while taking Vyvanse.
- CNS stimulants cause increases in blood pressure (mean increase about 2-4 mm Hg) and heart rate (mean increase about 3-6 bpm). Monitor all patients for tachycardia and hypertension.
- Exacerbation of Pre-existing Psychosis: May exacerbate symptoms of behavior disturbance and thought disorder in patients with a pre-existing psychotic disorder. Induction of a Manic Episode in Patients with Bipolar Disorder: May induce a mixed/manic episode in patients with bipolar disorder. Prior to initiating treatment, screen for risk factors for developing a manic episode (e.g., comorbid or history of depressive symptoms, or a family history of suicide, bipolar disorder, and depression). New Psychotic or Manic Symptoms: At recommended doses, may cause psychotic or manic symptoms (e.g., hallucinations, delusional thinking, or mania) in patients with no prior history of psychotic illness or mania. Discontinue if symptoms occur.
- CNS stimulants have been associated with weight loss and slowing of growth rate in pediatric patients (monitor weight and height). Treatment may need to be interrupted in patients not growing or gaining weight as expected. Vyvanse is not approved for use in pediatric patients below 6 years of age.

**Contraindications**

- Patients with a history of drug or alcohol abuse or dependence.
- Hypersensitivity to amphetamines or other CNS stimulants, including Vyvanse, other amphetamine-containing products, and methylphenidate have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy.

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**Warnings and Precautions (continued)**

- **CNS stimulants, including Vyvanse, are associated with peripheral vasculopathy, including Raynaud’s phenomenon. Signs and symptoms are usually intermittent and mild; very rare sequelae include digital ulceration and/or soft tissue breakdown. Careful observation for digital changes is necessary during treatment with stimulants. Further evaluation may be required, including referral.**

- **Increased risk of serotonin syndrome when co-administered with serotonergic agents (e.g., SSRIs, SNRIs, triptans) and CYP2D6 inhibitors, but also during overdosage situations. Discontinue Vyvanse if it occurs and initiate supportive treatment.**

- **Adverse Reactions (continued)**

  - **Children aged 6 to 12:** decreased appetite, insomnia, upper abdominal pain, irritability, vomiting, decreased weight, nausea, dry mouth, and diziness;

  - **Adolescents aged 13 to 17:** decreased appetite, insomnia, and decreased weight;

  - **Adults:** decreased appetite, insomnia, dry mouth, diarrhea, nausea, anxiety, and anorexia.

- **Pregnancy and Lactation**

Vyvanse may cause fetal harm. Breastfeeding is not recommended during Vyvanse treatment.

**Please see accompanying Full Prescribing Information on following pages.**

**References:**

3. Data on file; SPD489-066; Shire US Inc.
4. Data on file; SPD489-067; Shire US Inc.
WARNING: ABUSE AND DEPENDENCE

VYVANSE® is contraindicated in patients with:

- Known hypersensitivity to amphetamine products or other ingredients of VYVANSE. Anaphylactic reactions, Stevens-Johnson Syndrome, angioedema, and urticaria have been observed in postmarketing reports.
- Patients taking monoamine oxidase inhibitors (MAOIs), or within 14 days of stopping MAOIs (including MAOIs such as linezolid or intravenous fentany), lithium, tramadol, tryptophan, buspirone, and St. John’s Wort. The co-administration with cytochrome P450 2D6 (CYP2D6) inhibitors may also increase the risk with increased exposure to the active metabolites of VYVANSE (d-amphetamines). In these situations, consider an alternative non-serotonergic drug or an alternative drug that does not inhibit CYP2D6.

VYVANSE® is contraindicated in pediatric patients treated with other CNS stimulants, including VYVANSE, other amphetamine-containing products, and methylphenidate, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy.

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Serotonin Syndrome

Serotonin syndrome, a potentially life-threatening reaction, may occur when amphetamines are used in combination with other drugs that affect the serotonin or norepinephrine systems such as monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John’s Wort. The co-administration with cytochrome P450 2D6 (CYP2D6) inhibitors may also increase the risk with increased exposure to the active metabolites of VYVANSE (d-amphetamines). In these situations, consider an alternative non-serotonergic drug or an alternative drug that does not inhibit CYP2D6.

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Concomitant use of VYVANSE with MAOIs drugs is contraindicated.

Discontinue treatment with VYVANSE® and any concomitant serotonergic agents immediately if symptoms of serotonin syndrome occur, and initiate supportive symptomatic treatment. If concomitant use of VYVANSE with other serotonergic drugs or CYP2D6 inhibitors is clinically warranted, initiate VYVANSE with lower doses, monitor patients for the emergence of serotonin syndrome during drug initiation or titration, and inform patients of the increased risk for serotonin syndrome.

ADVERSE REACTIONS

Clinical Trial Experience

Based on data from 4-week parallel-group controlled clinical studies of VYVANSE® in pediatric and adult patients with ADHD.

Adverse Reactions Associated with Discontinuation of Treatment

In the controlled trial in pediatric patients ages 6 to 12 years, 8% (18/218) of VYVANSE-treated patients discontinued due to adverse reactions compared to 0% (0/72) of placebo-treated patients. The most frequently reported adverse reactions leading to discontinuation (1% or more and twice rate of placebo) were decreased appetite (2/233; 1%) and insomnia (2/233; 1%).

In the controlled trial in pediatric patients ages 13 to 17 years, 3% (7/233) of VYVANSE-treated patients discontinued due to adverse reactions compared to 1% (1/77) of placebo-treated patients. The most frequently reported adverse reactions leading to discontinuation (1% or more and twice rate of placebo) were decreased appetite (2/233; 1%) and insomnia (2/233; 1%).

In the controlled adult trial, 6% (21/358) of VYVANSE-treated patients discontinued due to adverse reactions compared to 2% (1/62) of placebo-treated patients. The most frequently reported adverse reactions leading to discontinuation (1% or more and twice rate of placebo) were insomnia (8/358; 2%), tachycardia (358/358; 1%), insomnia (358/358; 1%), hypertension (4/358; 1%), headache (2/358; 1%), anxiety (2/358; 1%), and dyspnea (358/358; 1%).

Adverse Reactions Occurring at an Incidence of ≥5% or More Among VYVANSE® Treated Patients with ADHD in Clinical Trials

Most common adverse reactions (incidence ≥5% and at a rate at least twice placebo) reported in pediatric patients ages 6 to 17 years, and/or adults were anorexia, anxiety, decreased appetite, decreased weight, diarrhea, dizziness, dry mouth, irritability, insomnia, nausea, upper abdominal pain, and vomiting.

Adverse Reactions Occurring at an Incidence of ≥5% or More Among VYVANSE® Treated Patients with ADHD in Clinical Trials

Adverse reactions reported in the controlled trials in pediatric patients ages 6 to 12 years, pediatric patients ages 13 to 17 years, and adult patients treated with VYVANSE® or placebo:

- Adverse Reactions Reported by ≥2% of Pediatric Patients Ages 6 to 12 Years with ADHD Taking VYVANSE® and Greater than or Equal to Twice the Incidence in Patients Taking Placebo - VYVANSE® (n=218), Placebo (n=72):
  - Decreased Appetite (39%, 4%), Insomnia (23%, 3%), Abdominal Pain Upper (12%, 6%), Irritability (10%, 0%), Vomiting (5%, 4%) Weight Decreased (9%, 1%), Nausea (6%, 3%), Dry Mouth (5%, 0%), Dizziness (5%, 0%), Affect Lability (3%, 0%), Rash (3%, 0%), Pyrexia (2%, 1%), Somnolence (2%, 1%), Tic (2%, 0%), Anorexia (2%, 0%).

- Adverse Reactions Reported by ≥2% of Pediatric Patients Ages 13 to 17 Years with ADHD Taking VYVANSE® and Greater than or Equal to Twice the Incidence in Patients Taking Placebo - VYVANSE® (n=233), Placebo (n=77):
  - Decreased Appetite (34%, 3%), Insomnia (13%, 4%), Weight Decreased (9%, 0%), Dry Mouth (4%, 1%), Palpitations (2%, 1%), Anorexia (2%, 0%), Tremor (2%, 0%).

- Adverse Reactions Reported by ≥2% of Adult Patients with ADHD Taking VYVANSE® and Greater than or Equal to Twice the Incidence in Patients Taking Placebo - VYVANSE® (n=358), Placebo (n=62):
  - Decreased Appetite (39%, 4%), Insomnia (23%, 3%), Weight Decreased (9%, 0%), Dry Mouth (4%, 1%), Palpitations (2%, 1%), Anorexia (2%, 0%), Tremor (2%, 0%).
Decreased Appetite (27%, 2%), Insomnia (27%, 8%), Dry Mouth (26%, 3%), Diarrhea (7%, 0%), Nausea (7%, 0%), Anxiety (6%, 0%), Anorexia (5%, 0%), Feeling Jittery (4%, 0%), Agitation (3%, 0%), Increased Blood Pressure (3%, 0%), Hyperhidrosis (3%, 0%), Restlessness (3%, 0%), Decreased Weight (5%, 0%), Dyspnea (2%, 0%), Increased Heart Rate (2%, 0%), Tremor (2%, 0%), Palpitations (2%, 0%).

In addition, in the adult population erectile dysfunction was observed in 2.6% of males on VYVANSE and 0% on placebo; decreased libido was observed in 1.4% of subjects on VYVANSE and 0% on placebo.

Postmarketing Experience
The following adverse reactions have been identified during postapproval use of VYVANSE. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events are as follows: cardiomyopathy, mydriasis, diplopia, difficulties with visual accommodation, blurred vision, eosinophilic hepatitis, anaphylactic reaction, hypersensitivity, dyskinesia, dysgeusia, tics, bruxism, depression, dermatillomania, alopecia, aggression, Stevens-Johnson Syndrome, chest pain, angioedema, urticaria, seizures, libido changes, frequent or prolonged erections, constipation, and rhabdomyolysis.

DRUG INTERACTIONS
Clinically Important Interactions with Amphetamines

MAO Inhibitors (MAOIs)
Clinical Impact: MAOIs are sympathomimetic amines, increasing amphetamine metabolism, increasing adrenergic effects on the release of norepinephrine and other monoamines from adrenergic nerve endings causing headaches and other signs of hypertensive crisis. Toxic neurological effects and malignant hyperpyrexia can occur, sometimes with fatal results.

Intervention: Do not administer VYVANSE during or within 14 days following the administration of MAOIs [see Contraindications].

Serotonergic Drugs
Clinical Impact: The concomitant use of VYVANSE and serotonergic drugs increases the risk of serotonin syndrome.

Intervention: Initiate with lower doses and monitor patients for signs and symptoms of serotonin syndrome, particularly during VYVANSE initiation or dosage increase. If serotonin syndrome occurs, discontinue VYVANSE and the concomitant serotonergic drug(s) [see Warnings and Precautions].

CYP2D6 Inhibitors
Clinical Impact: The concomitant use of VYVANSE and CYP2D6 inhibitors may increase the exposure of dextroamphetamine, the active metabolite of VYVANSE compared to the use of the drug alone and increase the risk of serotonin syndrome.

Intervention: Initiate with lower doses and monitor patients for signs and symptoms of serotonin syndrome particularly during VYVANSE initiation and after a dosage increase. If serotonin syndrome occurs, discontinue VYVANSE and the CYP2D6 inhibitor [see Warnings and Precautions and Overdosage].

Urinary Acidifying Agents
Clinical Impact: Urinary acidifying agents can increase blood levels and potentiate the action of amphetamine.

Intervention: Co-administration of VYVANSE and urinary acidifying agents should be avoided.

Urinary Alkalinizing Agents
Clinical Impact: Urinary alkalinizing agents can increase blood levels and efficacy of amphetamines.

Intervention: Increase dose based on clinical response.

Tricyclic Antidepressants
Clinical Impact: May enhance the activity of tricyclic or sympathomimetic agents causing striking and sustained increases in the concentration of d-amphetamine in the brain; cardiovascular effects can be potentiated.

Intervention: Monitor frequently and adjust or use alternative therapy based on clinical response.

Drugs Having No Clinically Important Interactions with VYVANSE
From a pharmacokinetic perspective, no dose adjustment of VYVANSE is necessary when VYVANSE is co-administered with guanfacine, venlafaxine, or oxerutin. In addition, no dose adjustment of guanfacine or venlafaxine is needed when VYVANSE is co-administered.

From a pharmacokinetic perspective, no dose adjustment for drugs that are substrates of CYP1A2 (e.g. theophylline, duloxetine, melatonin), CYP2D6 (e.g. atomoxetine, desipramine, venlafaxine), CYP2C19 (e.g. omeprazole, lanoseratol, clozaam), and CYP3A4 (e.g. midazolam, pimozide, simvastatin) is necessary when VYVANSE is co-administered.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ADHD medications during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Psychostimulants at 1-866-961-2388 or visiting online at https://womensmentalhealth.org/clinical-and-researchprograms/pregnancyregistry/adhd-medications/.

Risk Summary
The limited available data from published literature and postmarketing reports on use of VYVANSE in pregnant women are not sufficient to inform a drug-associated risk for major birth defects and miscarriage. Adverse pregnancy outcomes, including premature delivery and low birth weight, have been seen in infants born to mothers dependent on amphetamines. Monitor infants born to mothers taking amphetamines for symptoms of withdrawal such as feeding difficulties, irritability, agitation, and excessive drowsiness.

Lactation

Lisdexamfetamine is a pro-drug of dextroamphetamine. Based on limited case reports in published literature, amphetamine (d-or L-) is present in human milk, at relative infant doses of 2% to 13.8% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 1.9 and 7.5. There are no reports of adverse effects on the breastfed infant. Long-term neurodevelopmental effects on infants from amphetamine exposure are unknown. It is possible that large doses of dextroamphetamine might interfere with milk production, especially in women whose lactation is not well established. Because of the potential for serious adverse reactions in nursing infants, including serious cardiovascular reactions, blood pressure and heart rate increase, suppression of growth, and peripheral vasculopathy, advise patients that breastfeeding is not recommended during treatment with VYVANSE.

Pediatric Use
Safety and effectiveness of VYVANSE have not been established in pediatric patients below the age of 6 years.

Geriatric Use
Clinical studies of VYVANSE did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Renal Impairment
Due to reduced clearance in patients with severe renal impairment (GFR 15 to <30 mL/min/1.73 m²), the maximum dose should not exceed 50 mg/day. The maximum recommended dose in ESRD (GFR <15 mL/min/1.73 m²) patients is 30 mg/day.

Lisdexamfetamine and d-amphetamine are not dialyzable.

DRUG ABUSE AND DEPENDENCE

VYVANSE contains lisdexamfetamine, a prodrug of amphetamine, a Schedule II controlled substance.

OVERDOSAGE

Consult with a Certified Poison Control Center (1-800-222-1222) for up-to-date guidance and advice for treatment of overdosage. Individual patient response to amphetamines varies widely. Toxic symptoms may occur idiosyncratically at low doses.

Manifestations of amphetamine overdose include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states, hypervigilance, and rhabdomyolysis. Fatigue and depression usually follow the central nervous system stimulation. Serotonin syndrome has been reported with amphetamine use, including VYVANSE. Other reactions include arrhythmias, hypertension or hypotension, circulatory collapse, nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning is usually preceded by convulsions and coma.

Lisdexamfetamine and d-amphetamine are not dialyzable.

Distributed by: Takeda Pharmaceuticals America, Inc., Lexington, MA 02421

Made in USA

For more information, go to www.VYVANSE.com or call 1-877-TAKEDA-7 (1-877-825-3327).

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Clozapine: Increased Risk of COVID-19 Severity?

CASE VIGNETTE

"Mr Brown" is a white male, aged 55 years, with a 30-year history of schizophrenia, hypertension, and hyperlipidemia. His schizophrenia has been stable for more than 25 years on clozapine. Five months ago, he was fully vaccinated against COVID-19. However, 1 month ago, he tested positive for COVID-19. Although he had no known infected contacts, his teenager had fatigue and rhinorrhea the preceding week. Mr Brown’s primary symptoms included loss of taste and smell, fatigue, and an occasional dry cough, which resolved within 7 days. He did not have any fever or shortness of breath, nor did he require emergency department or inpatient services. He continued taking clozapine under the advisement of his psychiatrist without complication. Other than over-the-counter analgesics and antitussives, he did not take any medications for COVID-19. Mr Brown quarantined for 10 days, and then resumed his usual activities without further sequelae.

Clozapine—the gold standard antipsychotic for treatment-resistant schizophrenia—may affect the innate immune system and is associated with increased risk of neutropenia and agranulocytosis.1 Clozapine may also affect the adaptive immune system, given its association with reduced levels of immunoglobulins.2 There is evidence that increased risk of infections, including viral infections like pneumonia, in patients treated with clozapine vs other antipsychotics.3 Severe COVID-19 infection can cause pneumonia, acute respiratory distress syndrome, and death. Also, several risk factors for severe COVID-19 infection, including older age, diabetes, and cardiovascular disease, are more prevalent in patients treated with clozapine.4

Current Research

Using a regional health care register, Ohlis and colleagues5 investigated whether patients treated with clozapine, compared with other antipsychotics, are at increased risk of more severe COVID-19 infection, as indexed by inpatient treatment, intensive care unit (ICU) care, or death. They included all residents in Stockholm County, Sweden—approximately 2 million total inhabitants—18 years or older by March 1, 2020, who had (1) a diagnosis of a psychotic disorder (in the preceding 14 months) and (2) been prescribed and dispensed antipsychotic medication during 2020. Exposure was defined as clozapine treatment, and those who were prescribed other antipsychotics were considered unexposed. The primary outcomes were inpatient or ICU care or death due to COVID-19 between March 1, 2020, and January 14, 2021. Data were analyzed using Cox proportional hazard ratios, controlling for effects of age, sex, residence, country of birth, socioeconomic status, number of care visits, and comorbid medical illness. A total of 8333 persons in Stockholm County met study inclusion/exclusion criteria, of whom 966 (12%) had received clozapine treatment. The mean subject age was 51 years, and 53% of subjects were male. Overall, 1.9% of clozapine-treated patients and 2.7% of other antipsychotic–treated patients experienced COVID-19–related inpatient care, ICU care, or death during the study period. After controlling for potential confounding factors, the hazard ratios (HRs) for inpatient care (HR, 0.96; 95% CI, 0.54-1.70), ICU care (HR, 1.69; 95% CI, 0.48-5.93), and death (HR, 0.86; 95% CI, 0.26-2.8) were not significantly different for patients treated with clozapine vs other antipsychotics.

Study Conclusions

The authors found no indications that clozapine treatment was associated with a more severe course of COVID-19 infection. Findings are consistent with other case series that did not find an association between COVID-19 infection and reduced neutrophil counts in patients treated with clozapine. Study strengths included the use of register data with comprehensive measures of many potential risks for severe illness. However, results should be interpreted with caution, given the small number of severe cases, which raises the possibility of inadequate study power. Data on length of antipsychotic treatment, and whether antipsychotics were withheld upon diagnosis of COVID-19, were also not available.

Concluding Thoughts

Findings support existing recommendations for sustained treatment with clozapine during the COVID-19 pandemic. Adverse psychiatric risks of discontinuing clozapine treatment likely outweigh the risks of continued treatment with careful monitoring.

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

REFERENCES
Malingering as a Maladaptive Pattern of Survival During the Pandemic

SECTION EDITOR James Bourgeois, OD, MD
Teofilo Matos Santana, MD; Matthew N. Goldenberg, MD, MSc, and Seth Powsner, MD

Malinger is a common challenge for emergency department (ED) clinicians (Figure), and disasters such as the COVID-19 pandemic tip more people into such dysfunctional adaptations. We present 3 cases of COVID-19–induced malingering.

Malingering: The Diagnosis
DSM-5 describes malingering as “the intentional production of false or grossly exaggerated physical or psychological problems.” More specifically, malingering is a conscious deceptive behavior employed episodically and opportunistically. The feigning, simulation, or exaggeration of symptoms is dimensional and continuous rather than an absolute condition. Suspected secondary gains include food and shelter, medications, financial gains, and avoidance of jail, work, or family responsibilities. In the absence of traditional and reliable psychiatric symptoms, and given the presence of the manipulative features described, malingering is not always considered a legitimate psychiatric disorder.

Although malingering in psychiatric emergency settings has not been widely studied, colleagues in a New York City academic hospital found that malingering was suspected among one-third of the patients presenting to the psychiatric ED. Other assessments in urban psychiatric EDs have suggested that 13% were strongly or definitely suspected of feigning symptoms. Malingering also poses a challenge to emergency medicine physicians, who, for example, need to differentiate between patients who need pain medications and those who fabricate pain symptoms to obtain medications.

A sophisticated psychiatric assessment should differentiate malingering from its often parallel condition factitious disorder, in which deception also occurs voluntarily and consciously. In factitious disorder, however, motivation remains unconscious, with an aim of emotional compensation rather than financial or external advantage.

Psychiatrists are often insufficiently trained in the assessment of malingering and factitious disorders. They and their staff can become conflicted around its diagnosis and management. Patients themselves, however, are rarely concerned with diagnostic fine points or validity. When they have needs to fulfill, especially basic needs, that becomes their goal. A psychiatric evaluation aimed at diagnostic clarity fundamentally conflicts with the patient’s goal. Once malingering has been diagnosed, what is a just course of action during a pandemic?

Once malingering has been diagnosed, what is a just course of action during a pandemic?

Subsequently, John returned. In fact, after the COVID-19 lockdown, he presented 12 times for complaints including chest pain, seizures, and suicidal ideation. He had only come to the ED twice in the months prior to the lockdown. At his visits before lockdown, he was straightforward and explained that he needed medications for his seizure disorder.

Psychiatry staff—physicians and a licensed clinical social worker (LCSW)—decided to take a different approach at one of his later visits. They realized John was frustrated that the state office closures prevented him from obtaining ID documents, an insurance card, or money, and that the travel restrictions prevented his return to the state where he was living. The psychiatry LCSW gave him a sleeping bag, bus passes, and food, and instructed him to reconnect with a case worker in the community. John returned 2 hours later, after scratching his wrist superficially. In retrospect, it was too late in the day to find a place to bed down. He reconstituted overnight and asked to be discharged in the morning.

CASE 1
“John,” a man in his 50s, returned to Connecticut in February 2020 after living elsewhere for years. He came to our ED reporting seizures; he was noted to be dismissive and uncooperative, which led to a psychiatric referral. Psychiatric staff noted that John’s suicidal plans kept changing from cutting his wrist to stabbing his abdomen with a stick, and then to walking in traffic. The combination of his vague symptoms, confrontational response when asked for details, and lack of a traditional psychiatric history led staff to believe that his main problem was housing. He was held overnight in our observation area due to his general level of distress. John apologized the next morning for his confrontational behavior, showed a complete resolution of symptoms, then requested discharge.

Figure. Characteristics of Patients Highly Suspect of Malingering in an ED

CASE 2
“A month into the pandemic, “James,” a middle-aged man, was noted to be loitering in our ED waiting area. Triage staff asked him to register so that
he could talk to a social worker. A social worker dis- covered that James did not have much social support, but, until the pandemic, he had seemingly been able to subsist in the community. A review of his chart revealed a history of substance abuse, homelessness, and legal problems, but no traditional psychiatric history. On interviewing James, the social work department found him to be angry, even talking of killing people. James was referred to the psychiatry ED.

On psychiatric evaluation, instead of being “de- pressed,” James said that his “father died recently of COVID in Florida.” His affect was not congruent with his story. The psychiatrist also noted that he started asking for admission to the hospital even before the interview was complete. Further into the interview, James threatened to “kill Chinese people,” alluding to the coronavirus originating in Wuhan. Although the psychiatrist doubted the patient’s behavior was the product of mental illness, given the provocative statement, James was kept in the ED for observation overnight. By morning, it became evident that he did not have acute psychiatric symptoms—he did not appear to be in any significant distress. He was laughing with other patients and demanding various things of staff. He was then discharged.

James returned to our ED a few days later, saying he was angry that no one was helping him. Now he threatened to “kill myself or somebody else.” He gave no details and no plan. He was thought to be malingering for housing. He was again discharged.

Similar presentations continued over the next week until he tested positive for COVID-19 (while minimally symptomatic). This test result made him eligible for a designated COVID-19–positive shelter. From there, James was transferred to a government-subsidized hotel room. His ED presentations ceased for 10 days.

Unfortunately, the hotel evicted James when he was reported to be inviting people into his room to use drugs. He then returned to our ED. Upon again being discharged, James declared “If I have to, I will use illegal means to get what I need, and I will keep coming back to the ED.”

Malingering: The Context

Yale New Haven Hospital (YNHH) is a 1500-bed tertiary care medical center that operates 2 EDs in downtown New Haven, Connecticut, handling about 80,000 visits a year. They include psychiatric emergency services (PES) staffed 24 hours a day with locked space for 22 patients with psychiatric issues, plus a locked psychiatric observation unit with capacity for 16 patients.

Connecticut Governor Ned Lamont issued emergency orders suspending nonessential business and ordering residents to stay at home shortly after Connecticut reported its first COVID-19 case on March 8, 2020. YNHH instituted COVID-19–specific triage, admission, and discharge algorithms. It also implemented visitor restrictions, stricter hand hygiene, face masks, and temperature monitoring. Accessibility is inherent to the ED mission: The ED at YNHH did not raise any new barriers to access.

The crisis caused state offices to close, preventing John from Case 1 from obtaining an ID card, Medicaid coverage, funds, work, or housing. It also affected shelter facilities: Services were suspended and patients were referred to (limited) government-subsidized hotel rooms. Opioid treatment programs restricted their services. Community activity programs and soup kitchens cut back to avoid social gathering. All this left both John and James with very few options. These patients came to our ED due to lack of any support—the local social safety net was in tatters.

The individuals in these cases also suffered from the indirect effects of business closures. People in the community were now unable to support others in need. There was growing fear of viral contagion. Some families shut out their own family members out of fear that elderly parents were at risk. Patients with unstable housing who used to fall back on family in the past were now literally left out in the cold.

Fundamentally, these patients were seeking shelter in our ED because of the pandemic. Despite our efforts as psychiatrists to be helpful, we were not effective because these patients were not seeking psychiatric help. When John was given concrete assistance (bus passes, sleeping bag), it reduced some of his need for the ED. Of note, once rested and fed, both patients exercised enough self-control to obtain their discharge, use drugs, and start all over again. Substance cravings motivated more of their behavior than we realized at the time. Staff became so frustrated that one typed, “Inappropriate use of mental health resources during time of a health crisis is an unacceptable way of getting his needs met,” in John’s record.

Malingering: The Deal

Where but in the United States is there an urban society without a secure social safety net that also offers “intensive medical services” all day and night for all comers? Lack of a social alternative doubly strains the overwhelmed US health care system. For such patients, a PES or general ED is not a health care facility—it is simply a potential source of food, accommodation, psychoactive substances, or something else whose lack has become critical, especially during a disaster. In the words of an ED social worker, “An ED is a 24-hour social service agency.”

Before the pandemic, we had an equilibrium. We had an implicit deal: “We’ll give you a hand with food and shelter during this cold night, but you leave in the morning.” In point of fact, hospitals are usually paid whether or not a patient is malingering. Other, more legitimate diagnoses may justify the charges (eg, adjustment disorder or substance-induced mood disorder).

The equilibrium was also changed by reduced utilization of emergency services and hospitalization. Even patients with strokes and heart attacks avoided hospitals out of fear of COVID-19 in the early stages of the pandemic. Preliminary assessments in our health system suggest a decline of 30% of psychiatric ED visits during the first weeks of the pandemic. This pandemic challenged physicians to revisit their ideology, convictions, and values, consciously or unconsciously.

“James returned to our ED a few days later, saying he was angry that no one was helping him. Now he threatened to ‘kill myself or somebody else.’”

CASE 3

“...He is full of it, doctor,” the triage nurse announced when this patient presented. “Jack” was in his 20s and originally from the West Coast. He had come to the psychiatric ED’s attention 3 days after he arrived downtown on a train from New York City. Prior to the pandemic, he had survived in New York City for 8 months by panhandling. Now, from our town green, he called 911 to report a man having a seizure. EMS deduced that he was calling about himself during the so-called seizure. They brought Jack to our ED anyway because he told them he was homeless and sad and wanted to talk to someone.

During the psychiatric assessment, he was dismissive, vague, and very inconsistent. “Can’t you tell that I’m hearing voices?” Jack said while covering his face with a blanket. After resting for 5 hours, he was discharged.

Three hours later, after the sun had set, police brought him back to the ED; this time, it was from the
It is important to see beyond patients’ deceptions and fell into malingering. It was not until the pandemic disrupted Jack’s habitat, prompting him to be faced with the reality of malingering.

Two hours later, he was arrested and taken into police custody. Jack explained that he had stolen a knife from a drugstore and attempted to rob 2 downtown restaurants. This time, our interviewer noticed significant disorganization. Jack was upset and paranoid about New York City and about his family. He was not only happy that he had been arrested because he would be safe in jail; in fact, he was asking to be discharged to jail.

A call to Jack’s mother revealed a diagnosis of schizophrenia. She also described methamphetamine-use disorder starting at age 16, and more recent synthetic marijuana use. With this information, it seemed more appropriate to involuntarily admit the patient to a psychiatric facility. COVID-19 testing was negative.

Malingering and psychiatric illness can coexist and often do. Our clinicians had to see past the malingering to recognize psychotic and substance use disorders. What is also interesting is the way in which the pandemic disrupted Jack’s habit, prompting him to board a train as far as he could easily travel. He was even more poorly adapted to these new circumstances and fell into malingering.

Concluding Thoughts

It is important to see beyond patients’ deceptions to identify solutions to real problems while assessing and treating malingering patients in the context of a natural disaster. This challenge is compounded by negative countertransference, if only from added work, combined with manipulation. Physicians may need to walk a fine line between collusion and confrontation.

More studies of the malingering patient in the ED might be helpful. An institutional approach or a policy may facilitate the management and hopefully decrease the frequency of the maladaptive behavior.10 All these efforts would help ED staff; they may help decrease the time spent with these patients and may reduce frustration or burnout.

This COVID-19 pandemic presents an unexpected opportunity to observe behavioral adaptation to crisis and to consider the medical-ethical dilemmas that arise. Focusing on patients who mangle highlights subtle issues of justice and beneficence and challenges us to avoid overcompensation and generalization in our response.

Malingering is not a distinctively different phenomenon during the pandemic. However, this pandemic has been a distinct precipitant—for scarce resources, governmental restrictions, and fear of infection. Patients and ED staff are all on edge, which affects decision-making and ultimately clinical outcomes.

Dr Matos Santana is an assistant professor of psychiatry at Yale School of Medicine in New Haven, Connecticut, and physician lead for Psychiatric Emergency Services at Yale New Haven Hospital. Dr Goldenberg is an associate professor of psychiatry at Yale School of Medicine and co-director of the Medical Student Clerkship.

REFERENCES
**NEW INDICATIONS**

**NOW APPROVED**

for adults with

**BIPOLAR DEPRESSION:**

**BIPOLAR I OR II**

CAPLYTA is the first and only bipolar depression treatment indicated for both bipolar type I or II as monotherapy and adjunctive therapy with lithium or valproate\(^1\)

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There are no head-to-head clinical studies comparing the safety and efficacy of these products. This chart is descriptive of the FDA-approved indications.

- CAPLYTA is also indicated for schizophrenia in adults\(^1\)

CAPLYTA is indicated in adults for the treatment of schizophrenia and depressive episodes associated with bipolar I or II disorder (bipolar depression), as monotherapy and as adjunctive therapy with lithium or valproate.

**Important Safety Information**

**Boxed Warnings:**
- Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. CAPLYTA is not approved for the treatment of patients with dementia-related psychosis.
- Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric and young adults in short-term studies. Closely monitor all antidepressant-treated patients for clinical worsening, and for emergence of suicidal thoughts and behaviors. The safety and effectiveness of CAPLYTA have not been established in pediatric patients.

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

**Warnings & Precautions:** Antipsychotic drugs have been reported to cause:
- **Neuroleptic Malignant Syndrome**, which is a potentially fatal reaction. Signs and symptoms include hyperpyrexia, muscle rigidity, delirium, autonomic instability, elevated creatinine phosphokinase, myoglobinuria (and/or rhabdomyolysis), and acute renal failure. Manage with immediate discontinuation of CAPLYTA and provide intensive symptomatic treatment and monitoring.
- **Tardive Dyskinesia (TD),** a syndrome of potentially irreversible, dyskinetic, and involuntary movements which may increase as the duration of treatment and total cumulative dose increases. The syndrome can develop after a relatively brief treatment period, even at low doses, or after treatment discontinuation. Given these considerations, CAPLYTA should be prescribed in a manner most likely to reduce the risk of TD. Discontinue CAPLYTA if clinically appropriate.
- **Metabolic Changes,** including hyperglycemia, diabetes mellitus, dyslipidemia, and weight gain. Hyperglycemia, in some cases extreme and associated with ketoadipsis, hyperosmolar coma or death, has been reported in patients treated with antipsychotics. Measure weight and assess fasting plasma glucose and lipids when initiating CAPLYTA and monitor periodically during long-term treatment.
- **Leukopenia, Neutropenia, and Agranulocytosis (including fatal cases),** Perform complete blood counts in patients with pre-existing low white blood cell count (WBC) or history of leukopenia or neutropenia. Discontinue CAPLYTA if clinically significant decline in WBC occurs in absence of other causative factors.

**CAPLYTA**

**Am J Psychiatry**

50:12, 2013


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**including stroke and transient ischemic attacks have been established in pediatric patients.**

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**Cariprazine**

**Lurasidone**

**Quetiapine/Quetiapine XR**

**Antipsychotic drugs have been reported to cause:**

- Neuroleptic Malignant Syndrome, which is a potentially fatal syndrome of potentially irreversible, a delayed-onset, and possibly fatal neurologic complication in patients treated with antipsychotic drugs. The syndrome can develop after a relatively brief treatment period, even with therapeutic doses of antipsychotic drugs, and may occur even after treatment is discontinued. The syndrome has not been reported with CAPLYTA.

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

**Falls.** CAPLYTA may cause somnolence, postural hypotension, and motor and/or sensory instability, which may lead to falls and, consequently, fractures and other injuries. Assess patients for risk when using CAPLYTA.

**Seizures.** Use CAPLYTA cautiously in patients with a history of seizures or with conditions that lower seizure threshold.

**Potential for Cognitive and Motor Impairment.** Advise patients to use caution when operating machinery or motor vehicles until they know how CAPLYTA affects them.

**Body Temperature Dysregulation.** Use CAPLYTA with caution in patients who may experience conditions that may increase core body temperature such as strenuous exercise, extreme heat, dehydration, or concomitant anticholinergics.

**Dysphagia.** Use CAPLYTA with caution in patients at risk for aspiration.

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

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

**Adverse Reactions:** The most common adverse reactions in clinical trials with CAPLYTA vs placebo were:

- Schizophrenia: somnolence/sedation (24% vs 10%) and dry mouth (6% vs 2%)
- Bipolar Depression (Monotherapy, Adjunctive therapy); somnolence/sedation (13% vs 3%, 13% vs 3%), dizziness (8% vs 4%, 11% vs 2%), nausea (8% vs 3%, 9% vs 4%), and dry mouth (5% vs 1%, 5% vs 1%)

**Scan the code or visit caplytahcp.com to learn more about titration-free, once-daily CAPLYTA**

**Statistically significant improvement as monotherapy or as adjunctive therapy with lithium or valproate**

**Monotherapy**

**Adjunctive with Lithium or Valproate**

**Placebo**

**Placebo**

**•** CAPLYTA showed a statistically significant improvement in both MADRS total score and the key secondary endpoints (CGI-BP-S total score in Study 1 and CGI-BP-S depression score in Study 2) at week 6.

**References:**


CAPLYTA is a registered trademark of Intra-Cellular Therapies, Inc. © 2021 Intra-Cellular Therapies, Inc. All rights reserved. 12/2021 US-CAP-2100528
DOSAGE AND ADMINISTRATION

CAPLYTA is indicated for the treatment of schizophrenia in adults and depressive episodes associated with bipolar I or II disorder (bipolar depression) in adults, as monotherapy and as an adjunctive therapy with lithium or valproate.

INDICATIONS AND USAGE

CAPLYTA is indicated for the treatment of schizophrenia in adults and depressive episodes associated with bipolar I or II disorder (bipolar depression) in adults, as monotherapy and as an adjunctive therapy with lithium or valproate.

CONTRAINDICATIONS

Avoid use of CAPLYTA in patients with known hypersensitivity reaction to lumateperone. Reactions have included pruitus, rash (e.g., allergic dermatitis, papular rash, and generalized rash), and urticaria.

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS: AND SUICIDAL THOUGHTS AND BEHAVIORS

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

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

Suicidal Thoughts and Behaviors

Antidepressant Increased risk of suicidal thoughts and behaviors, and in pediatric patients with schizophrenia, the risk appears to be highest among the elderly, especially elderly women, but it is not possible to predict which patients are likely to develop the syndrome. Whether antidepressant drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of tardive dyskinesia and the likelihood that it will become irreversible increase with the duration of treatment and the cumulative dose. The syndrome can develop after a relatively brief treatment period, even at low doses. It may also occur after discontinuation of treatment.

Tardive Dyskinesia: Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements that may develop in patients treated with antipsychotic drugs. The risk appears to be highest among the elderly, especially elderly women, but it is not possible to predict which patients are likely to develop the syndrome. Whether antidepressant drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of tardive dyskinesia and the likelihood that it will become irreversible increase with the duration of treatment and the cumulative dose. The syndrome can develop after a relatively brief treatment period, even at low doses. It may also occur after discontinuation of treatment.

Tardive dyskinesia may remit, partially or completely, if antipsychotic treatment is discontinued. Antipsychotic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome, possibly masking the underlying process. The effect that symptomatic suppression has upon the long-term course of tardive dyskinesia is unknown.

Given these considerations, CAPLYTA should be prescribed in a manner most likely to reduce the risk of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients: (1) who suffer from a chronic illness requiring long-term antipsychotic treatment and (2) for whom alternative, effective, and potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, use the lowest dose and the shortest duration of treatment producing a satisfactory clinical response. Periodically reassess the need for continued treatment.
Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Antipsychotic drugs, including CAPLYTA, should be used cautiously in patients at risk for aspiration.

ADVERSE REACTIONS

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

The safety of CAPLYTA has been evaluated in placebo-controlled clinical trials in 2664 adult patients with schizophrenia. However, some patients may require treatment with CAPLYTA despite the presence of the syndrome.

If signs and symptoms of tardive dyskinesia appear in a patient on CAPLYTA, drug discontinuation should be considered. Tardive dyskinesia may remit, partially or completely, if antipsychotic treatment is discontinued. Antipsychotic treatment at low doses. It may also occur after discontinuation of treatment.

Monitor all antidepressant-treated patients for any indication for clinical worsening and emergence of suicidal thoughts or behaviors.

Bipolar Depression - Mania

The following findings are based on the pooled short-term (6-week), placebo-controlled monotherapy bipolar depression studies in adult patients treated with CAPLYTA administered at a daily dose of 42 mg (N=372).

There was no single adverse reaction leading to discontinuation that occurred at a rate of ≥2% in CAPLYTA-treated patients.

The most common adverse reactions (incidence of at least 7% of patients exposed to CAPLYTA and greater than twice the rate of placebo) were somnolence, dizziness, nausea, and dry mouth.

Bipolar Depression - Adjunctive Therapy with Lithium or Valproate - The following findings are based on a 6-week, double-blind, placebo-controlled, add-on therapy study in adult patients with bipolar disorder.

Bipolar Depression - Mean Changes from Baseline:

In the 6-week, monotherapy bipolar depression trials, the frequency of reported events related to extrapyramidal symptoms (EPS), including akathisia, extrapyramidal disorder, muscle spasms, restlessness, muscularisclonic stiffness, dyskinesia, dystonia, muscle twitching, tardive dyskinesia, tremor, drooling, and urinary retention was 3.7% for CAPLYTA and 2.4% for placebo.

In the 4- to 6-week schizophrenia trials, the mean changes from baseline for CAPLYTA-treated patients and placebo-treated patients were 0.1 and 0 for the SAS, -0.1 and 0 for the BARS, and 0.1 and 0 for the AIMS, respectively.

Bipolar Depression - In the 6-week, monotherapy bipolar depression trials, the frequency of reported reactions related to EPS, including muscle spasms, dyskinesia, extrapyramidal disorder, movement disorder, tremor, restlessness, and akathisia was 1.3% for CAPLYTA and 1.1% for placebo.

Bipolar Depression - In the 6-week, adjunctive therapy bipolar depression trial, the frequency of reported reactions related to EPS, including muscle spasms, akathisia, extrapyramidal disorder, gait disturbance, and restlessness was 4.0% for CAPLYTA and 2.3% for placebo.

In the 6-week, monotherapy bipolar depression trials, the mean changes from baseline for CAPLYTA-treated patients and placebo-treated patients were 0.1 and 0 for the SAS, -0.1 and 0 for the BARS, and 0 and 0 for the AIMS, respectively.

Drug Interactions

Concomitant Use with Other Drugs: Concomitant use of CAPLYTA with moderate or strong CYP3A4 inhibitors may increase lumateperone exposure, which may increase the risk of adverse reactions. Concomitant use of CAPLYTA with moderate or strong CYP3A4 inhibitors includes: Aliskiren, Drotrecogin alfa, Empagliflozin, Ivermectin, linezolid, Loxapine, Midazolam, Nelfinavir, Olanzapine, Perampanel, Pimobendan, Pizotifen, Rivastigmine, Ritonavir, St. John’s wort, voriconazole, Ziprasidone, and Zolpidem.

Concomitant Use of Other Drugs: Concomitant use of CAPLYTA with CYP3A4 inhibitors (other than strong CYP3A4 inhibitors) that are not known to induce CYP3A4 (e.g., Cimetidine, Fosamprenavir, Itraconazole, Risperidone, Pimozide, Quinidine) may increase lumateperone exposure. Concomitant use of CAPLYTA with CYP3A4 inducers may decrease lumateperone exposure.
Gilding the Goldwater Lily

James L. Knoll IV, MD

Psychiatry and politics do not have a history of mixing well. In 1972, democratic presidential nominee George McGovern briefly considered US Senator Thomas Eagleton as his vice-presidential nominee. Despite Eagleton’s impressive record of being the youngest Missouri attorney general in the state’s history at age 31, McGovern requested that Eagleton withdraw as his nominee. Why? For the simple reason that Eagleton was known to have voluntarily sought effective treatment for depression. Yet the damage was done, as McGovern’s opponents used the opportunity to question the soundness of his judgment in selecting Eagleton. One wonders how such a scenario might play out today. Would society be more enlightened or would we repeat this pattern of weaponizing mental health?

My esteemed colleagues assert that the Goldwater Rule (GWR) is “fine,” but in need of refinement. Having addressed the GWR before, I will be mercifully brief—particularly because I would like to introduce a new set of unofficial “rules” that I hope will bring clarity to a debate that has been ongoing for some 50 years. My colleagues do well in quoting a favorite Bob Dylan song about the changing times. Yet the weight of change is often counterbalanced with the time-worn aphorism plus ça change, plus c’est la même chose. Even in this era of social media and information overload, human nature remains the same. Students of human nature will recognize how little has changed since American Psychiatric Association President Daniel Blain, MD, denounced such “professional opinions” many years ago, calling them a “low blow to all who would work to advance the treatment and care of the mentally ill of America.”

Since the inception of the GWR, the pushback and boundary-blurring around it has neither resulted in any appreciable “helpful knowledge” nor served to “improve the community and better the public health.” By now, it is painfully apparent that most advocates of liberalizing or abolishing the GWR are motivated by political partisanship. The temptation is evidently too great for us to avoid using the mantle of our profession to stigmatize a political figure with pejorative labels.

The examples given by my colleagues seem generally unrealistic insofar as easily observable symptoms are very likely to be attended to by those who will see them long before the public would. Any “refinements” notwithstanding, it still seems implausible that a psychiatrist who (1) has not examined a sitting US president and (2) has no access to that president’s private health care information is in a position to make psychiatric diagnoses or conduct risk assessments on that president.

At the end of the day, we are left with mere speculation based on symptoms observed in a nonclinical, time-limited setting. The speculation typically amounts to a tallying of perceived character flaws—not public education about serious mental illness. My psychodynamic training, now quite out of fashion, compels me to dwell a moment on my colleagues’ repeated use of negatives (eg, “I do not want to speculate…”). I commend them for acknowledging this, as some may be so bold as to claim they are not speculating at all. They have “seen the movie,” so to speak—they have confirmed their findings via multiple news media clips and have been able to amass a check-list of findings to prove their point. However, enumerating symptoms and criteria of a particular diagnosis, without explicitly stating that diagnosis, seems questionable. It allows one to speculate right up to the line and point to the diagnosis from inches away without touching it or speaking its name.

All this begs the question: Why do psychiatrists continue to wrestle with the GWR as though it is either obsolete or in need of change? Is it because our brave new world demands a retrofitting of a longstanding APA ethics rule? Has ubiquitous video monitoring abrogated the need for a personal exam and record review? Or perhaps, having vanquished all mental suffering, we have become restless and wish to set our sights higher. A noble goal indeed. Yet in practice, it seems GWR violators are primarily focused on spotting character flaws they believe voters are too unenlightened to perceive.

Having said my piece about the GWR, for what I hope is the last time, I am now prepared to roll out what I should like to call the Knoll–Water Rules:

1. GWR violations damage the credibility of psychiatry.
2. GWR violations have not appreciably improved public trust of psychiatry (see rule 1).
3. When psychiatric terms, diagnoses, or medical authority are used to express opinions in public media about political figures without examining them, look for a political agenda.
4. Psychiatrists are poorly able to depoliticize their opinions in public media about political figures. This rule is immutable regardless of how the GWR might be revised.
5. GWR violations involving a US president have resulted in neither a cornucopia of public health benefits nor increased public appreciation of the importance of mental health. Other approaches to achieving these goals are highly recommended.
6. Duty-to-protect and Tarasoff-type laws apply to patients being treated by psychiatrists—not to US presidents with whom one has no doctor-patient relationship. Should a US president require civil commitment, an appropriate state hospital psychiatrist will surely be provided.
7. Accomplished individuals have been known to have character flaws. This applies to both US presidents and psychiatrists.
8. The GWR does not prevent psychiatrists from engaging in political activism—as US citizens.

In sum, it seems to me that the GWR is fine. Period. No refinements needed. Passionate advocacy may be best redirected to improving mental health care in the United States. As excellent as one’s diagnostic skills from afar may be, one might remember the 25th Amendment and take some comfort in the fact that the president’s cabinet, the vice president, Congress, the chief White House physician, and the entire White House medical unit are likely to be in a slightly better position to observe concerning signs and, if necessary, recommend an emergent course of cognitive therapy and mindfulness training.

Dr Knoll is a professor of psychiatry and director of forensic psychiatry at SUNY Upstate Medical University in Syracuse, New York, and clinical director of Central New York Psychiatric Center in Marcy, New York. He is Emeritus Editor in Chief of Psychiatric Times™ and president-elect of the American Academy of Psychiatry and the Law (2022-2023).

REFERENCES
The Goldwater Rule Needs Refinement to Reach Its Goal

Alan D. Blotcky, PhD

First, I appreciate Dr Knoll’s time and effort in responding to our article. Frank discussion about an issue or matter is always healthier than silence or stubborn withdrawal. In our country today, there is far too little conversation between individuals who have opposing views. I am glad that as mental health professionals we are being role models for open and respectful dialogue that can lead to a deeper understanding and a search for common ground.

Second, today we have access to hundreds, if not thousands, of hours of political figures’ speeches, interviews, books, recordings, tweets, and much more. We also have research showing that clinical interviews, while very important, should not be the sole basis of a diagnostic formulation. In truth, rarely—if ever—do we base our diagnostic decisions solely on an interview. Nor should we.

Third, a stated mission of psychiatry is the betterment of society and improvement in public health. As such, psychiatry must change and adapt to the times. Ethical guidelines are not meant to be static and fixed in a vacuum detached from community and societal changes.

Fourth, our 5 refinements to the Goldwater Rule do not give permission for the definitive diagnosis of a public or political figure without professional contact. That, for certain, is our common ground.

Fifth, “character flaws” do not equate with personality disorder. If a psychiatrist or a psychologist is competent and experienced, he or she knows that a personality disorder is diagnosed based on a variety of criteria, one of which is problematic and maladaptive behavior vis-à-vis others. No well-trained, competent, and experienced psychiatrist or psychologist would—or should—politicize a medical or psychiatric illness by simply focusing on “character flaws.” Flip, inflammatory, or pejorative comments are unacceptable. But personality disorders are real, definable, and well-researched entities.

Sixth, all psychiatrists and psychologists should already know that any professional comment in the public domain or otherwise must be accurate, scientifically based, measured, balanced, within one’s area of expertise, and with a recognition of one’s limitations. If that ethical standard is broken, the professional should be reprimanded strongly.

I want to reiterate what we asserted in our original article. The mission of psychiatry is to better society and improve public health. That mission cannot be accomplished in a clinician’s office. It requires contact with the community, often through the press. There must be ethical ways for psychiatrists and other professionals to achieve this stated mission. After all, we are the ones who are experts on mental processes, pathological behavior, disturbed family and group relationships, problems in communities, and ills in society. Let us take on this mission in a full-throated way, not shy away from it.

I believe the best way for psychiatry as a profession to enhance its credibility is for psychiatrists to show their competence, expertise, and reliance on scientific underpinnings in dealing with community and public health matters. Credibility cannot be achieved by retreating into one’s office and blocking out the world. We need to be visible, expressive, helpful, and responsible.

One final comment: If psychiatrists are supposed to better society and improve public health, then serious occasions call for—may, require—comment and opinion. I believe all mental health professionals have a duty and responsibility to warn the public if, for example, democracy is being overturned in real time. That is exactly what we faced 1 year ago. Psychiatry could have improved its credibility and standing had it engaged with the scary and potentially tragic reality of January 6, 2021. Instead, in my opinion, psychiatrists and psychologists looked weak and inconsequential in their collective silence. How sad for our field. What a missed opportunity. I believe the Goldwater Rule needs to be refined so that psychiatry and psychiatrists can achieve their overarching mission: to better society and improve public health. It is an achievable mission.

Dr Blotcky is a clinical and forensic psychologist in private practice in Birmingham, Alabama. He is also a clinical associate professor in the Department of Psychology at the University of Alabama at Birmingham.

REFERENCE

The Right to Comment With Respect and Dignity

Ronald W. Pies, MD

Thanks to my friend and colleague, Dr Knoll, for his comments, which I find lighthearted but serious in purpose. Readers may recall that Dr Knoll and I coauthored an article on the Goldwater Rule and, in most respects, we share a similar perspective. What follows is not a rebuttal of Dr Knoll’s commentary, but an elaboration of why I believe the Goldwater Rule needs to be illuminated, not eliminated. More centrally, I want to clarify my views on psychiatric diagnosis in general. First, though, I want to thank Dr Blotcky for inviting me to participate in this article, and Dr Moffic for his many contributions advocating a wider role for psychiatrists in societal and community issues. I completely agree with them that this is an important part of psychiatry’s mission.

My coauthors and I charted a “middle way” between the 2 poles of either eliminating the Goldwater Rule or keeping it as is, as Dr Knoll wishes. My hope is that the 5 ways we outlined will help psychiatrists apply the Goldwater Rule, particularly when members of the media ask us to comment on living public figures. The 2 hypothetical vignettes in our article are, to be sure, idealized cases, but I do not regard them as unrealistic.
It is clear from several articles and books that many psychiatrists regard the Goldwater Rule as a kind of “gag rule.” I understand their frustration with the Goldwater Rule in its present “unrefined” form. But as Dr Knoll and I have argued, the Goldwater Rule does not gag psychiatrists from speaking out against injurious or dangerous policies on the part of government or its officials; rather, it defines the conditions under which psychiatrists may render a professional opinion via a public figure—and that requires a professional psychiatric evaluation.

To be sure, a public figure’s tweets, speeches, and observable interactions with others can provide useful insights into the individual’s psychology and personality, but a professional psychiatric opinion cannot be rendered solely on the basis of such external data. In my view, many charismatic public figures adopt a persona that may seem dramatic, impulsive, or even a bit unhinged, but do so for political or other strategic purposes—hence the well-known expression “crazy as a fox.”

It is only through a deep understanding of a person’s developmental issues, ego defenses, interpersonal conflicts, family life, and so on that a professional diagnostic opinion can emerge. This also entails a process of diagnostic rule-outs. For example, the DSM-5 criteria for a personality disorder require that 1) there is evidence of “significant distress or impairment in social, occupational, or other important areas of functioning”; 2) the enduring pattern of behavior is not better explained by another mental disorder (e.g., a mood disorder); and 3) the behavioral pattern is not attributable to substance abuse or an underlying medical condition. There is simply no way these rule-outs can be investigated properly, absent a thorough clinical evaluation.

I am aware of critiques pointing out deficiencies in the direct interview, and I do not claim that a single, clinical assessment is an infallible guide to diagnosis. Often, in my experience, a patient’s diagnosis will not emerge until 2, 3, or even more evaluative sessions have been completed, sometimes augmented by interviews of family members, imaging studies, a review of school records, and psychometric or neuropsychiatric testing. But limitations and deficiencies in our present gold standard of evaluation are no argument for diagnosing public figures—or pronouncing on their “dangerousness”—without a comprehensive clinical evaluation. Tweets, speeches, and public appearances may sometimes be useful adjuncts to the standard clinical evaluation, but they are no replacement for it.

On the other hand, I believe it is professionally appropriate and consistent with the Goldwater Rule for psychiatrists to offer a differential diagnosis of a set of signs, symptoms, and behaviors, absent a clinical evaluation—but, in my view, only if the differential diagnosis is uncoupled from the public figure in question. That is why, in our article, the responses to hypothetical media queries were phrased so impersonally. Yes, I know: Some in the media will portray this practice as merely a coy or covert way of diagnosing a public figure. Such misrepresentation is not something psychiatrists can easily control, but we can control our adherence to professional standards.

Indeed, as Dr Moffic wisely observed in 2016, “All of us have the right to comment on behaviors we observe and to voice our political opinions—but, from the mental health perspective, such rights should be exercised with respect and dignity.”

Dr Pies is professor emeritus of psychiatry and a lecturer on bioethics and humanities at SUNY Upstate Medical University in Syracuse, New York. He is also a clinical professor of psychiatry at Tufts University School of Medicine in Boston, Massachusetts, and Editor in Chief Emeritus of Psychiatric Times.

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The Moffic-Gold Rules

H. Steven Moffic, MD

Although Dr Knoll concludes in his commentary that the Goldwater Rule is fine, period, by rolling out his Knoll-Water Rules, be instead conveys that they are inadequate as is. In that spirit, I would like to provide 8 comparative points to those he provides, but from the perspective of refining the Goldwater Rule. Although mine are meant to stand on their own, they are best appreciated in this discussion next to those of Dr Knoll, one by one. May our sets of new rules evoke more needed discussion and reconsideration on this controversy.

1. Psychiatry is in need of credibly and ethically “contributing to the improvement of the community and the betterment of public health.” Participating more often in the discussion of various public issues that call for psychiatric expertise is one of the many ways to do so, as, for example, I have attempted to do in the weekday daily columns and weekly videos on Psychiatry and Society for Psychiatric Times.

2. That a recent book on a political figure became a bestseller and led in short order to an expanded edition suggests that the public is strongly interested in the opinions of psychiatrists. The challenge is how best to convey these without violating the current Goldwater Rule.

3. Without commenting on individual public figures, certain psychiatric disorders, such as personality disorders, by their very nature have symptoms that may be more readily seen in public interaction with other people than in an individual diagnostic evaluation.

4. Psychiatrists are trained to reduce the intrusion of personal opinions into their professional opinions by examining their own countertransference reactions.

5. Because the Goldwater Rule has inhibited psychiatrists from speaking out about US presidents, we do not know how helpful it might be for the restraints to be loosened without allowing for what Freud called wild analysis.

6. Whether the Tarasoff-type laws of risk to others can apply to public figures who are not patients may need a test case. Given the challenges of diagnosing and treating VIPs, the usual processes of civil commitment may be compromised and special social psychiatric expertise required.

7. In all professions, including politics and psychiatry, character flaws and psychiatric disorders may be helpful or harmful to those in leadership positions, as another bestseller by a psychiatrist has shown.

8. Although psychiatrists may claim to be making political opinions solely from the standpoint of a citizen, the public may assume that it is a professional opinion unless the professional role is hidden or unknown.

Dr Moffic is an award-winning psychiatrist who specializes in the cultural and ethical aspects of psychiatry. A prolific writer and speaker, he received the one-time designation of Hero of Public Psychiatry from the Assembly of the American Psychiatric Association in 2002. He is retired from his tenured professorship at the Medical College of Wisconsin in Milwaukee.

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COMMENTARY

To Disclose or Not to Disclose?
Lessons From a Dying Therapist

Orli Avi-Yonah, PhD; and Shannon T. Woolley, EdD

This article is dedicated to the memory of Sharland Trotter, EdD, whose wisdom, courage, and generosity gave life to this project.

What can we learn about practicing while dying from a therapist who is terminally ill? In this article, we examine this wisdom in an interview generously given by the brilliant therapist Sharland Trotter, EdD, 3 weeks before her untimely death. In the interview, Trotter shared her experiences and insights while treating patients for 3 years between her diagnosis with metastatic colon cancer in 1994 and her passing on Thanksgiving Day 1997.

The literature on this subject focuses primarily on the question of when and to what extent a therapist diagnosed with terminal illness should disclose this fact to their patients. Contrary to the majority view in the literature at the time of her death, but in accordance with emerging views that have gradually become widely accepted, Trotter adopted a policy of maximal disclosure consistent with the patients’ needs from the moment she was diagnosed. The broader clinical implications of Trotter’s insights are discussed.

Exploring Literature

Most articles about the therapist who is terminally ill are written from the patient’s perspective. The few articles written from the therapist’s perspective mostly focus on serious illness from which the therapist ultimately recovered, with Feinsilver—also argues in favor of disclosure, for and against self-disclosure, but suggests that there is an ethical duty to disclose within limits. The only previous paper by a dying therapist—Feinsilver—also argues in favor of disclosure, which functions in dialectical interplay with fantas
dy therapist. They emphasize the analyst’s defense against acknowledging their mortality and the gradual development of acceptance. They counsel a limited disclosure that varies from patient to patient. Pinsky argues for a return to Freud’s more essential, humane approach against the emphasis of later analysts on neutrality, abstinence, and termination.

An emerging perspective on disclosure is in Elliott and Ragsdale, which concerns mental illness in therapists. The study found that expressions of prejudice toward people with mental illnesses were common among these mental health professionals and may contribute to an inclination among therapists to reveal their mental health history selectively, if at all, on the job. When it comes to sharing with clients, therapists tended to be thoughtful and deliberate about self-disclosure, only using it when they believed it would be beneficial to the client rather than to themselves. Regardless of whether they shared with clients, most of the therapists emphasized that having direct experience with mental illness enhanced their ability to empathize with their clients, cautioning that sometimes empathy triggered their own symptoms.

An important issue that is not sufficiently discussed in the literature is how disclosure affects planning for the transfer of patients to other therapists, and the problems that arise if there is no disclosure. Hackett explains that the myth of the untroubled therapist is shattered all too soon with the unexpected news of a therapist’s death following a short illness or due to incident or accident. These kinds of unplanned terminations have been demonstrated to result in a range of damaging effects on clients, outlined in the Table. Further, Barbanel found that therapists who “inherit” clients whose previous therapist died often experience negative comparisons with the deceased therapist, and that therapeutic attachment is not as secure.

Betrayal of trust
• Complex mourning
• Despair
• Self-disclosure

TABLE. Damaging Effects of Unplanned Terminations on Clients

These feelings may include:

• Ultimate abandonment
• Hostility
• Depersonalization
• Somaticization

The most recent essays contained in Masur and Damaging development of acceptance. They counsel a limited disclosure that varies from patient to patient. Pinsky argues for a return to Freud’s more essential, humane approach against the emphasis of later analysts on neutrality, abstinence, and termination.

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Because of these negative effects, Hackett explains, international and US codes of ethics mandate provisions for the sudden death or incapacita-
tation of therapists and supervisors. Some organizations with such codes of ethics include the American Counseling Association, the American Psychological Association (APA), the European Association for Counselling, and the Irish Association for Counselling and Psychotherapy. However, only the APA provides tools and resources that therapists can use to deliver on this obligation. Practical and legal matters also arise following a therapist’s death. These include the implications of intestacy and demands on surviving family members to notify key individuals, as well as their duties as executor/administrator of the deceased clinician’s estate.

The Therapist’s Perspective
This interview with Trotter was conducted by the coauthors of this article in Trotter’s home while she received home hospice care. The following text is verbatim by Trotter, but it has been edited for confidentiality.

BACKGROUND. I wanted to somehow get this recorded, my work over the last 3 years with patients, as I have been dying of colon cancer, metastatic colon cancer. I was diagnosed in the fall of 1994. It involved surgery to remove the offending tumor and then chemotherapy.

RELATIONSHIP WITH SUPERVISOR. I am extremely fortunate in having had a sort of mentor, supervisor, senior consultant who really helped me in doing well under the circumstances. And it was very honest about this. That, without, burdening my patients, I was going to answer their questions and not be equivocal. And allow them to be—to take part in their own stuff and not get into it—not get into, “Well, you can’t do anything ‘til we’ve talked.” And I went to his office on a Saturday morning, the Saturday after Thanksgiving. And we went through my patient list one by one. And we discussed how much information this one needed to know, how much information that one needed to know, how I should phrase it.

DISCLOSURE. The bottom line is that I told everyone that I was having surgery. And if they asked further, I told them as many details as they asked for, probably holding back on some details.

So that was the beginning. That began a policy in my practice, which had been an underlying assumption until then, that I was going to be very honest about this. That, without, burdening my patients, I was going to answer their questions and not be equivocal. And allow them to be—to take part in this process with me. It had many unintended side effects as I sort of practiced what I would say to people. For example, “Well, have you asked about [weight loss]? Might have something to do with your diet.” I said, “Well, no, I haven’t.” He said, “Well, maybe it does, and maybe there’s a connection.” So, I would ask, and he would gently push me. Wherever I saw in the material of therapy a possibility that it was connected to my death, I would pursue it. I tried—and I think largely succeeded in—not rubbing anybody’s nose in this.

Surprisingly, only a few of my patients initially terminated. Most of them have hung in there for however many years I’ve been seeing them and these 3 years of illness.

PATIENTS’ REACTIONS. For each of them, I think it has meant something different. It has stirred up their own feelings of loss and abandonment, and we have talked about prior losses of theirs. It has reinforced their attachment to me in a very good way. As I began, over the last several months, to actually terminate with people formally, I asked if they thought—what they thought about this experience. What they thought about having been in therapy with somebody who is dying. Whether they thought it had been a burden or a damage to them. And every single one of them said it had been a growth experience rather than anything else.

MISTAKES MADE. Inadvertently, I pushed it beyond where I should have pushed it. I should have terminated with most people at the end of August. I wanted to somehow get this recorded, my work over the last 3 years with patients, as I have been dying of colon cancer, metastatic colon cancer. I was diagnosed in the fall of 1994. It involved surgery to remove the offending tumor and then chemotherapy.

RELATIONSHIP TO CHILDREN. Another way that the supervisor’s insistence on the kind of straightforwardness helped me was, I realized suddenly if I were talking to my patients in this candid way, I needed to be talking to my children in an equally candid way. So, it opened the door to an ongoing series of conversations with my own children, which continues, and in which I can see their growth and their coming to terms with this in ways that I would not have anticipated.

DISCOMFORT WITH DISCLOSURE. This leads us into the whole conversation about self-disclosure and when do you self-disclose and when do you not. Are there ever any times when disclosing something personal about your own life is good for the patient? And actually, at the beginning of my illness, I read that literature. And I finally decided that I really could not do or be anything other than I am, who I am, and how I operate. So immediately it became clear to me that I could not suddenly shift gears and become the silent therapist, the blank screen, the—you know. And although I think there is something to be said for not disclosing anything of your personal life to your patients, I think there is also a great danger of disclosing too much. And disclosing without knowing consciously what this may do to the patient—what this may stir up in the patient. So, I struggled with that, and immediately it was clear to me that if I was going to err, it would be on the side of self-disclosure, not on the side of silence.

And there is the issue that you asked about: How many people wanted to know? And it is a very interesting question because some people wanted to know a lot, and some people would say, “How are you doing?” And I would say, “I’m actually doing well under the circumstances.” And they would say, “That’s good,” and then turn to their own stuff and not get into it—not get into, “Well, tell me more about what you’re experiencing.” They did not really want to know the details, and obviously I did not want to force the details down their throats.

DISCOMFORT WITH DISCLOSURE. There were patients who wanted to know what I considered too much—too much clinical information. And I told them I did not think the information would help them in any way.

RELATIONSHIP WITH PREDIAGNOSIS PRACTICES. [Let’s say] I was sitting here, [amongst] a debate. People on one side argue that no self-disclosure is ever good, that there is too much risk in letting the patient know anything much about you. On the other side are the people who argue you can tell patients almost anything. [I see it like this]: With each patient, I try to assess, well, what is this information going to really do to and for the patient? Is this something that they really need to know? And is it a thing that they—it would not make any differ-
ence if they knew? For example, “Where am I going on vacation?” I have no problem saying, “I’m going to blah blah blah. I’m going to the beach.” “How many kids do I have? How old are they?” It would be a little hard to hide in my circumstance, since I have a husband who writes a column for the [Boston] Globe. Most of my patients know about that, and probably most of them read it or at least glance at it or at least are aware that it is there. So already they know a little bit about my personal life.

My practice is in my house, so they know a lot just taking in the circumstances—you know, what the house looks like. So, yeah, I struggled with self-disclosure to some extent. I think one always has to. I think you cannot make a blanket policy and have that just be your policy and never be so inflexible that it does not change. [even] if that is what seems indicated. And sometimes not telling somebody something, even if it would not really in the long range make a difference, is important.

**Effects of Physical Illness.** I canceled very few sessions, and I also made a real effort to hang on to my patients. They rarely said “Are you feeling sleepy?” because I would nod off. And I would say, “Yes, I am.” And apologize. By that point, it was so clear that the illness was gaining ground that it did not bear a lot of discussion. Although as we sit here, talking about it, I think I should have said, “What is this like for you, you know, sitting here with a therapist who’s falling asleep?” I did not. So that is one I missed. In some ways, I was surprised to find there was such a big debate about this in the literature. I never needed to excuse myself. I remember one incident—and it felt like being in hell—not knowing whether I was going to make it, willing my body to stay tight until the end of the session. In other cases, I canceled. I mean, if I knew it would be a huge risk, I canceled.

**Patients who did not want to know.** It was interesting to me. I mean, it added a dimension to a portrait of them that I was developing in my head as the therapy went on: that people were capable of sitting there and, really, talking about their problems. But the therapists would work the summer to make it right. I mean, to say goodbye to each other. So, in that case, my denial again sort of guided me—or my lack of denial. The fading away of denial guided me in, “OK, what is the next clinical step here?” I think I made some mistakes. I think some patients who I saw practically until the bitter end, I held out to them some ambiguous hope that maybe it would be longer, and I think that was a mistake. Because it would have been clearer and cleaner if, earlier on, we had set a termination date and had done it, but we did not. So, there was a little bit of ambiguity at the end with these people in particular.

**Epilogue**

Trotter’s generosity, straightforwardness, and honesty offer a road map for navigating the tragic reality of the therapist’s untimely death. Trotter discusses her attempts to collect information about her patients’ perception of the course of their therapy and highlights the important role of the therapist’s professional support system as she navigated the process of dying while working. Her unique perspective on the debate around issues of self-disclosure calls for the therapist’s engagement with a rigorous process of self-reflection governed by the age-old question of whose needs are being met in the therapy, and what is the role of the therapist’s professional life in the larger context of their identity.

Dr Avi-Yonah is a teaching associate in psychiatry at Cambridge Health Alliance, Harvard Medical School. Dr Woolley works in grief support services for Samaritans of Boston. The authors report no known conflicts of interest.

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A daily occurrence in the practice of most psychiatrists is designing a cross-titration schedule to change a patient’s medication regimen from one antipsychotic to another. The possible reasons for this cross-titration are many and are listed in Table 1. Since the US Food and Drug Administration (FDA) approval of chlorpromazine in 1954, our armamentarium of antipsychotic medications has grown significantly, and each antipsychotic has unique properties that should be considered once the decision has been made to change antipsychotic medications.

There is no single correct way to perform this cross-titration, and the approaches used in clinical practice vary considerably. This article will review 10 important factors to consider when cross-titrating from one antipsychotic (drug A: the drug that is being tapered and discontinued) to another antipsychotic (drug B: the drug that is being initiated and titrated upward as the new antipsychotic) to maximize success and minimize complications. The ultimate goal is to provide the patient with the experience of a smooth transition to increase the likelihood of a successful cross-titration and maximize the patient’s compliance with this change in antipsychotic.

Ten factors stand out as meriting serious consideration when cross-titrating antipsychotics, and each will be explored in detail. These are listed in Table 2. Historically, 3 general approaches have been used to cross-titrate from 1 antipsychotic to another: abrupt, brief overlapping, and gradual overlapping.

1. Baseline Antipsychotic Plasma Level

The published recommendations of these approaches over the decades are confounded by 1 important missing detail: What was the antipsychotic plasma level of drug A on day 1 of this cross-titration? Over the past 5 years, significant attention has been directed at the importance of obtaining a baseline antipsychotic plasma level before any treatment modifications are made.2,4

The current standard is to obtain a 12-hour postdose plasma level, once at steady state (5 half-lives [t1/2s]) for oral antipsychotics, and a long-acting injectable antipsychotic serum level 1 to 72 hours before an injection once at steady state.5

Although for most antipsychotics there is no...
well-defined therapeutic range, a great deal of information can be gleaned from the resulting level obtained. Interpretation of the level depends on a range of clinical factors as well as the drug delivery system of the antipsychotic. The interested reader is directed to the recently published comprehensive handbook entitled “The Clinical Use of Antipsychotic Plasma Levels.”

If the antipsychotic plasma level of drug A is undetectable, it is reasonable in many circumstances to begin drug B in the same manner as a new start. However, there are exceptions to this, such as antipsychotics with very short t½s, which may be technically absent from the plasma, but could still result in specific withdrawal symptoms depending on the pharmacodynamics of the drug (for example, antihistamine and anticholinergic withdrawal, as well as withdrawal dyskinesia). If the antipsychotic plasma level of drug A is in the low range and there is a high confidence of patient drug compliance, increasing drug A’s dose and allowing for an adequate trial should be the next step. Many variables can result in a subtherapeutic drug level in the context of patient compliance. If the antipsychotic plasma level is in an accepted therapeutic range for an adequate duration, drug A can be considered a failed trial, and cross-titrating to a new antipsychotic is recommended.

2. Pharmacodynamic Differences

Chlorpromazine revolutionized the treatment of psychotic disorders in the United States in 1954, resulting in the first massive wave of deinstitutionalization of patients from numerous psychiatric hospitals. Remarkably, it was 3 years later, in 1957, that Katharine Montagu became the first scientist to confirm the presence of dopamine in the human brain. The activity of dopamine as a neurotransmitter was demonstrated the next year by Arvid Carlsson, MD, PhD. Following the completion of the sequencing of the 3 billion base pairs in the human genome in 2003, all 5 dopamine receptors have been identified and characterized. Elegant research in neuropsychiatry, including PET scans on live human brains in the presence of various concentrations of an antipsychotic along with the dopamine-2 receptor (D₂R) antagonist radioisotope C-11 raclopride, have consistently demonstrated that a functional antagonism of 65% to 75% of D₂Rs seems to be the sweet spot of antagonism to treat psychosis and mania.

Similar progress has simultaneously led to the classification and understanding of other neurotransmitter systems that are involved in drug-receptor activity by chlorpromazine and all the subsequent antipsychotics. Significantly, each antipsychotic has a unique receptor binding profile at the many subreceptors that are in play with the various antipsychotics. The common neurotransmitter systems that can be impacted include dopamine, norepinephrine (α and β subreceptors), serotonin, histamine, and muscarinic cholinergic, just to name the most significant.

Knowing the binding affinities at these differences defining the various receptor inhibition constants for antipsychotic drugs.

3. Half-Life Differences

Antipsychotics have a wide range of t½s; these predict how long it will take for drug A to leave the body once discontinued, and how long it will take for drug B to achieve steady state once at its target dose. Table 4 lists the t½s for many of the antipsychotic drugs, including their active metabolites when relevant. In general, after 5 t½s at the target dose, a drug has reached 97% of its steady-state level. Similarly, once a drug is discontinued, in 5 t½s, 97% of the drug will have been eliminated from the patient’s body. Exceptions to this include long-acting injectable antipsychotics, as well as drugs that have active metabolites that build up over time and contribute significantly to the pharmacological activity of that drug.

An extreme example would be cross-titrating from quetiapine to cariprazine, or vice versa. Both drugs have active metabolites, which need to be factored into the cross-titration. Excluding pharmacodynamic differences, which are significant, the t½ characteristics of quetiapine and cariprazine—including their active metabolites—are dramatically different. Quetiapine is metabolized immediately to the active metabolite N-desalkyl quetiapine, and both molecules contribute to its putative mechanism of action. Once at steady state, the mean area under the curve (AUC) and mean maximum concentration (Cmax) of N-desalkyl quetiapine are approximately 21% to 27% and 46% to 56%, respectively, of quetiapine itself. Quetiapine’s t½ is 6 hours, while N-desalkyl quetiapine’s t½ is 12 hours. Hence, steady state of both molecules will be reached by 60 hours.

Cariprazine, on the other hand, has 2 active metabolites, of which the second—didesmethyl cariprazine—gradually increases its plasma level over the first 4 to 6 weeks once cariprazine is begun, or after a dosage increase. At steady state,
Drug A is an “apine” (clozapine, olanzapine, quetiapine, asenapine). Drug B is an “odone” (risperidone, paliperidone, ziprasidone, lurasidone, iloperidone).

All the apines have significant antihistamine activity, whereas all the odones have negligible antihistamine activity. Rapidly tapering off an apine can lead to antihistamine withdrawal, which the patient can experience as insomnia, activation, and anxiety.

All of the apines, except asenapine, have significant anticholinergic activity, whereas all of the odones have negligible anticholinergic activity. Rapidly tapering off an apine can lead to anticholinergic withdrawal, which the patient can experience as hypersalivation, diarrhea, gastric cramping, and flu-like symptoms.

Drug A is an antagonist (all antipsychotics are antagonists except the 3 listed as a drug A). Drug B is an antagonist/partial agonist (i.e., aripiprazole, brexpiprazole, cariprazine).

If drug B is increased too quickly and drug A resulted in greater than 70% antagonism at the D₂R, this can induce psychosis or withdrawal dyskinesia. The binding affinities (inhibition constants) of all 3 of the antagonist/partial agonists are more potent than those of all the pure antagonists, but they are limited in the functional antagonism that they provide. This is demonstrated by the fact that none of the 3 antagonist/partial agonists elevate prolactin, as they are unable to achieve functional D₂R antagonism greater than approximately 70%. All the pure antagonists, if dosed high enough, can achieve 100% D₂R antagonism and have the potential to raise prolactin.

Antagonists/partial agonists, when serving as drug B, should be started in low dosages and gradually increased, allowing for the brain to accommodate to the decreasing functional D₂R antagonism as drug A is tapered and discontinued.

Table 3. Clinical Examples of Pharmacodynamic Differences to Inform Cross-Titration

1. Drug A is an “apine” (clozapine, olanzapine, quetiapine, asenapine). Drug B is an “odone” (risperidone, paliperidone, ziprasidone, lurasidone, iloperidone).

2. Drug A is an antagonist (all antipsychotics are antagonists except the 3 listed as a drug A). Drug B is an antagonist/partial agonist (i.e., aripiprazole, brexpiprazole, cariprazine).

If drug B is increased too quickly and drug A resulted in greater than 70% antagonism at the D₂R, this can induce psychosis or withdrawal dyskinesia. The binding affinities (inhibition constants) of all 3 of the antagonist/partial agonists are more potent than those of all the pure antagonists, but they are limited in the functional antagonism that they provide. This is demonstrated by the fact that none of the 3 antagonist/partial agonists elevate prolactin, as they are unable to achieve functional D₂R antagonism greater than approximately 70%. All the pure antagonists, if dosed high enough, can achieve 100% D₂R antagonism and have the potential to raise prolactin.

Antagonists/partial agonists, when serving as drug B, should be started in low dosages and gradually increased, allowing for the brain to accommodate to the decreasing functional D₂R antagonism as drug A is tapered and discontinued.

4. Metabolic Pathways Involved

First-pass metabolism occurs primarily in the liver, but with some drugs, it begins while crossing the intestines into the portal vein on its way to the liver. In humans, approximately 60 different cytochrome P450 (CYP) metabolic enzymes have been identified and characterized. Of these, the 3 most important in the metabolism of antipsychotics are CYP1A2, CYP2D6, and CYP3A4. Antipsychotics themselves have minimal effects on inhibiting or inducing CYP enzymes, but they can be significantly affected by other medications.

When planning a cross-titration, it is important to review with the patient all the prescription medications, over-the-counter medications, vitamins, food supplements, exposure to smoke, and ingestion of certain food items (such as grapefruit) before planning your medication choice and titration strategy. Information gleaned from this history can inform decisions on which drugs are the best options to be drug B, and potential changes in pharmacokinetics to be mindful of in drug A.

Clozapine and olanzapine are both primarily metabolized by CYP1A2. In addition to potential drug-drug interactions, CYP1A2 is significantly induced by smoke of any type, including smoke from cigarettes (nicotine is not involved in CYP1A2 induction). When starting either of these medications in an in-patient setting where smoking is not allowed (patients are often offered a nicotine patch), once stabilized and prior to discharge, it is useful to obtain a 12-hour postdose plasma level. Upon discharge, the patient will likely resume smoking, which will slowly induce CYP1A2 over the next several weeks. A repeat 12-hour postdose antipsychotic plasma level 2 weeks after discharge can be compared with the predischARGE level when the patient was stable, and the appropriate dose adjustment can be made. This may very well prevent a psychotic relapse.

CYP2D6 is a common metabolic pathway for several antipsychotics, and it has the largest number of genetic polymorphisms of any CYP enzyme (approximately 100 different alleles). Significantly, 3 antidepressants that are commonly coprescribed in patients on antipsychotics are fluoxetine, paroxetine, and bupropion—all 3 of which are potent inhibitors of CYP2D6. It is well established that these 3 antidepressants can convert a CYP2D6 extensive metabolizer to a poor metabolizer, which would result in prolonging the t½ of the antipsychotic and increasing its serum level. This example demonstrates the value of obtaining an antipsychotic plasma level to determine the patient’s actual plasma level, rather than guessing from a pharmacogenomic test that will provide only the patient’s genotype, not their functional phenotype.

The most common CYP pathway for all prescription drugs is CYP3A4. Such is the case for many antipsychotics. There are numerous inhibitors and inducers of CYP3A4, including grapefruit juice (depending on the concentration of furanocoumarins in a particular grapefruit strain) as a potentially potent inhibitor, and St. John’s wort as a potent inducer (similar to carbamazepine). Numerous prescription drugs have varying inhibitory and inducing effects on CYP3A4, which can be found in a good drug-interaction program.

Hence, knowing the metabolic pathway of drug A and drug B, along with all of the potential molecules that can impact that pathway, can provide important information when designing a cross-titration strategy.

5. Dose of Drug A Compared With Usual Dose Range of Drug A

Although a drug’s FDA-approved product insert provides a range of dosages recommended for each drug in each indication, the rule in clinical practice is that the prescriber finds the ideal dose through trial and error. The goal is always maximal benefit with minimal adverse effects, and over time, an attempt should be made to find the lowest effective dose of all medications. As a result of numerous patient-specific factors—including, among others, pharmacokinetic and pharmacodynamic variables, genetic vulnerabilities, drug absorption, cardiac output, renal and biliary excretion, P-glycoprotein heterogeneity, age, gender, and body mass index—2 patients who look exactly the same in most of these factors may still require very different dosages to achieve efficacy from the same drug.

As a proxy of sorts, the dose of drug A that has stabilized the patient relative to the usual dose of drug A that it takes to stabilize an average patient on that same drug for that same indication should be considered when constructing a cross-titration to a new antipsychotic. If the dose is significantly lower or higher than that for similar patients, the prescriber should attempt to determine the factors that contributed to this unusual dose, and determine whether these same factors will apply to drug B.

“Knowing the metabolic pathway of drug A and drug B can provide important information when designing a cross-titration strategy.”
6. **Length of Time on Drug A**

In a typical community mental health center practice, some long-term patients have been prescribed the same antipsychotic for years or longer. Other patients may have been on their current antipsychotic for several months. With our growing understanding of the brain’s neuroplasticity and constant rewiring through synaptogenesis, it intuitively makes sense that the longer a person has been on the same medication, the more that medication is integrated into the neurophysiology of the brain. Although speculative, it seems reasonable that, if clinically possible, the longer the patient has been taking a specific medication, the slower the cross-titration should be. This is a possible approach if the reason for antipsychotic cross-titration is due to a nonemergent factor. Possibilities include changing antipsychotics to decrease adverse events that impact quality of life and may be reversed by changing antipsychotics. Morbidities including weight gain, somnolence/sedation, hyperlipidemia, onset of prediabetes or frank diabetes, hyperprolactinemia, drug-induced movement disorders, cognitive impairment, residual psychotic symptoms, uncontrolled affective symptoms, or vague dysphoria may improve and possibly resolve with a change in antipsychotics. In this setting, a well-documented risk/benefit/adverse effect discussion with the patient/guardian should occur prior to the change.

7. **Acuity of Target Symptoms**

Often the clinical circumstances do not allow for a gradual and ideal cross-titration of antipsychotics. When a patient presents with severe acute symptoms and the prescriber determines that an immediate antipsychotic change is required, a more rapid antipsychotic cross-titration may be necessary. However, even in this situation, the 9 other factors should be reviewed. If drug A has receptor activity that drug B lacks, such as anticholinergic or antihistaminic properties, an attempt should still be made to taper drug A, albeit as fast as is clinically possible. Alternatively, if drug A must be discontinued and anticholinergic or antihistaminergic withdrawal symptoms occur, adding a non-antipsychotic such as diphenhydramine to prevent anticholinergic and antihistaminergic withdrawal can be considered.

The D₂R Ki’s and doses of drugs A and B should be reviewed, and the dosage of each drug throughout the cross-titration should be determined to minimize the likelihood of too much D₂R antagonism, which could lead to increased movement disorders, sedation, dysphoria, and increased risk for neuroleptic malignant syndrome acutely and tardive dyskinesia over the long term. On the other hand, if not enough D₂R antagonism is present during the cross-titration, the patient can have a relapse of psychotic symptoms or experience withdrawal dyskinesia.

If the decision is made to add an antagonist/partial agonist to replace a current pure antagonist, ensure that the likely current D₂R antagonism of drug A is equal to or less than what will result from the dose of drug B. If drug B is started at a dose to fully occupy the D₂R and drug A produced more D₂R antagonism than drug B can provide, the patient may experience an increase in psychosis or withdrawal dyskinesia. Additionally, all 3 of the antagonist/partial agonists have lengthy t½’s that, along with the potent binding affinity at the D₂Rs, will create a brain pharmacology that can not be easily reversed.

8. **Patient’s Motivation to Change From Drug A to Drug B**

As clinicians, one of our biggest challenges is to motivate our patients to adhere to their medication regimen, to tolerate side effects—some transient and some chronic—and to acknowledge that they have a mental illness that may benefit from their treatment plan. In a world where instant gratification rules the roost, it is even more difficult to convince our patients to move on to a second trial of medication after they failed to improve with an adequate dose for an adequate time on the first.

9. **Educating Patient/Guardian on Risks/Benefits of Cross-Titration**

Once a decision has been made to cross-titrate to a different antipsychotic, it is important to include the patient/guardian and all relevant support systems in a detailed discussion explaining the risks and benefits of this medication change, and to provide ample time for questions and discussion. When the patient/guardian and their support system feel included and respected during this process, there is a greater likelihood of participation, cooperation, and ultimate success with the transition to the new medication.

10. **Type of Delivery System of Drug A vs Drug B**

A variety of drug delivery systems exist for antipsychotics. Most antipsychotics are available in an oral formulation in tablet, capsule, and/or liquid forms. Quetiapine is also available in an extended-release form. Asenapine must be administered and absorbed sublingually because, if it is swallowed, it is inactivated by UGT-1A4, a metabolic enzyme in the gut. Asenapine is also available in a transdermal patch. Many antipsychotics are available for intramuscular injection. This allows for a more rapid onset of action and bypass of first pass metabolism in the liver.

Long-acting injectable antipsychotics (LAIA) are being used increasingly in the United States.¹ There are currently formulations for haloperidol, fluphenazine, risperidone, paliperidone, aripiprazole, and olanzapine. Injection frequency varies dramatically, from every 2 weeks to every 6 months. When cross-titrating on to or off of a LAIA, the pharmacokinetic properties differ across drug formulations, and the clinician should carefully review the product insert of the particular LAIA(s) being used.

**Novel Exception to Amount of D₂R Antagonism**

As often occurs in science, a finding is published that is inconsistent with established dogma, requiring us to refine our hypothesis. All antipsychotics that have been studied in live human brains for D₂R occupancy at various doses have demonstrated that their antipsychotic activity cor-

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### Table 4. Half-Lives (t½) of Common Antipsychotics

<table>
<thead>
<tr>
<th>Orally dosed antipsychotic</th>
<th>Half-life (t½) in hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>60-80</td>
</tr>
<tr>
<td>Asenapine</td>
<td>13-39</td>
</tr>
<tr>
<td>Brexiprazole</td>
<td>91</td>
</tr>
<tr>
<td>Cariprazine</td>
<td>48-120</td>
</tr>
<tr>
<td>Desmethyl-cariprazine</td>
<td>30-38</td>
</tr>
<tr>
<td>Didesmethyl-cariprazine</td>
<td>314-446</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>15-30</td>
</tr>
<tr>
<td>Clozapine</td>
<td>12-16</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>16</td>
</tr>
<tr>
<td>Haloperidone</td>
<td>12-36</td>
</tr>
<tr>
<td>Iloperidone</td>
<td>18-33</td>
</tr>
<tr>
<td>Loxapine</td>
<td>6-8</td>
</tr>
<tr>
<td>Lumateperone</td>
<td>18</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>20-40</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>30-60</td>
</tr>
<tr>
<td>Paliperidone (9-OH-risperidone)</td>
<td>17-23</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>8-12</td>
</tr>
<tr>
<td>Pimozide</td>
<td>23-43</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>6-11</td>
</tr>
<tr>
<td>N-desalkyl quetiapine</td>
<td>10-13</td>
</tr>
<tr>
<td>Risperidone</td>
<td>20-30</td>
</tr>
<tr>
<td>9-OH-risperidone (paliperidone)</td>
<td>17-23</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>4-8</td>
</tr>
</tbody>
</table>

¹Unless otherwise noted, adapted from reference 4.
²From Caplyta 2020 FDA-approved product insert.
³From Risperdal 2007 FDA approved product insert.
“If drug B is started at a dose to fully occupy the D_R and drug A produced more D_R antagonism than drug B can provide, the patient may experience an increase in psychosis or withdrawal dyskinesia.”

relates best when dosed so that their plasma level achieves between 60% and 80% of human brain D_R occupancy for at least 1 hour of every 24. The common protocol is to inject the radioisotope C-11 raclopride at Cmax of the antipsychotic and immediately perform a PET scan to look at percent binding of C-11 raclopride in contrast to its binding with no antipsychotic present. Clozapine andquetiapine, the 2 antipsychotics with the least potent inhibition constants at the D_R, have been shown to transiently occupy slightly more than 60% when dosed high enough (in the FDA-approved clinical dosage range). Some experts do opine that these 2 antipsychotics may provide efficacy below the usual 60% occupancy threshold.

Lumateperone, the newest FDA-approved antipsychotic for the treatment of schizophrenia, has demonstrated its clinical improvement in the Positive and Negative Syndrome Scale score by occupying only 39% of D_R at Cmax at the study dosage of 40 mg. Lumateperone is FDA approved only at the dose of 42 mg, which is its starting and treating dosage. The pharmacodynamics associated with this efficacy are not fully understood, but it has been hypothesized that lumateperone’s additional property of simultaneous partial agonism of the presynaptic D_R may contribute to its ability to provide an antipsychotic effect with low postsynaptic D_R antagonism. Theoretically, the partial agonism at the presynaptic D_R could decrease the release of presynaptic dopamine, hence creating less dopamine that needs to be blocked postsynaptically.17-18

Regardless of the pharmacodynamics, given lumateperone’s low D_R antagonism at its therapeutic and only dose of 42 mg, when cross-titrating to lumateperone, theoretically it should be able to be added on day 1 of the cross-titration, and then drug A will be slowly tapered off.

Concluding Thoughts
As is often the case in psychiatry, good clinical practice involves a solid understanding of the science of psychopharmacology as well as effective therapeutic skills and a healthy therapeutic alliance with the patient. The decision to cross-titrating from one antipsychotic to another should not be made lightly, as it will conclude a lengthy trial of drug A, with all the time, effort, and clinical acumen invested. Despite this, antipsychotic cross-titratations are a daily occurrence in all clinical psychiatric settings. The 10 factors presented in this article that should be considered before designing the cross-titration may increase the likelihood of a successful cross-titration.

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**San Joaquin County Behavioral Health Services** is seeking to fill Outpatient Adult [General], and Sub-Specialty Psychiatrist (Child Psychiatry, Geriatric, Forensic, Addiction and Psychosomatic Medicine) positions in a multidisciplinary, recovery-oriented clinical setting. Services are provided either on-site or using a hybrid model of on-site and tele-psychiatry practice. The positions offer a very competitive salary with a guaranteed base, plus incentive opportunities, board certified Psychiatrists have the potential to easily earn over 300K+ a year, competitive health insurance; up to three retirement and pension programs; 35 days of vacation and CME time that increase with tenure. Signing and moving bonuses are also available. Interested J-1 and H-1B candidates are welcome to apply. Fax your CV to (209) 468-2399 or email to BHSAdministration@sjcbs.org. EOE

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**PSYCHIATRIST NEEDED IN CALIFORNIA**

Come join a 20+ year-old successful child and adult psychiatry practice with a possibility of partnership or taking over the office of a retiring doctor. You will have the independence and flexibility of your work schedule both outpatient and inpatient consultation in a med-surg hospital. Opportunity to make more than $300,000 annually.

Please email your resume to: recruiting@soliguen.com

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**PSYCHIATRIC MEDICAL PRACTITIONERS, INC**

**OUTPATIENT Full-time TELE-PSYCHIATRY POSITION**

**BE/BC ADULT PSYCHIATRIST** licensed or willing to practice in CA, Practice from current State of Residence Candidate has to be EHR and Computer proficient. You will be doing Psychiatric Evals & Med Mgt of SMI patients in County MH Clinics. There is no On-Call. Income potential of $340-405K, plus CA Lic, DEA and Malpractice is paid, 1099 income. **Scan QR code for Apply:**

Send CV to Garewalmd@gmail.com, or Fax CV to (661) 368-0826

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**Hawaii**

**CHILD & ADOLESCENT MENTAL HEALTH DIVISION**

**PSYCHIATRIST** to work full-time in Santa Rosa, CA. Must have CA medical license or ability to obtain. Send CV to Mark David Levine, M.D., Professional Corporation 3835 N. Freeway Blvd., Ste 100, Sacramento, CA 95834 or email to: eowen@cpsych.com

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**PSYCHIATRIST** needed in California licensed Psychiatrists and Psychologists For details call 661-840-9270 or inquire with CV at jobs@telehealthdocs.com

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UMass Memorial Health and the University of Massachusetts Chan 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, Neuropsychiatry.

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

UMass Medical School

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

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

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

For additional information on the above, please contact:

Marie Hobart, MD, Vice Chair, Public Sector Psychiatry
Hatfield House, UMass Medical School
45 Lake Avenue North, Suite 501
Worcester, MA 01655
Phone: 508-856-3866
Fax (508) 856-3886
Email: Marie.Hobart@umassmed.edu

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

Massachusetts

MASSACHUSETTS

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Cape Cod, Massachusetts
Live and Work Oceanside

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

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

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

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

*Potential to be a full inpatient position if interested

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

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

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

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

Jolia Georges, Director of Physician Recruitment
Phone: 508-862-5481
jgeorges@capecodhealth.org

For more details about our position, please contact:

Jolia Georges, Director of Physician Recruitment
Phone: 508-862-5481
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Cape Fear Valley Behavioral Health Care’s mission is to meet and respond to the mental health needs of the community. We offer evidence-based, best practice treatments. Staffed by psychiatrists, psychologists, clinical social workers, psychiatric nurses, licensed professional counselors, and other mental health professionals, Cape Fear Valley Behavioral Health Care provides a team approach to mental wellness. Behavioral Health Care is accredited by The Joint Commission and licensed by the State of North Carolina.

The Health System is seeking providers for Disorder, and Mood Disorders is preferred. Additionally, ECT training and experience commitment to expand services:

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

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

**Child Outpatient Opportunity**
- BE/BC Child & Adolescent providers. The current structure is for 90% outpatient Monday through Friday work schedule.
- We offer best in class compensation plus generous benefits including Paid Malpractice, CME Time and Allowance, Accrued Paid Time Off, 401(k) 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

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 re-define 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 - Adult Staff Psychiatrist**
  (Belle Mead, NJ)
- **Inpatient - Raritan Bay Medical Center**
  (Perth Amboy, NJ)
- **Outpatient - Jersey Shore University Medical Center**
  (Neptune, NJ), Ocean Medical Center (Brick, NJ) and Southern Ocean Medical Center - (Manahawkin, NJ)
- **Medical Director for Adult Inpatient Unit**: Riverview Medical Center (Red Bank, NJ)
- **Outpatient Child & Adolescent Psychiatrist**: Hackensack University Medical Center (Hackensack, NJ) and Ocean University Medical Center (Brick, NJ)
- **Geriatric Psychiatry**: Hackensack University Medical Center (Hackensack, NJ)
- **Outpatient Addiction**: Jersey Shore University Medical Center (Neptune, NJ)

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

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The treatment of psychiatric disease is evolving with advances in imaging and genomic profiling and the emergence of investigational molecules as potential new treatments for prevalent psychiatric disorders. With these advancements it is important that psychiatrists, along with members of the multidisciplinary care team, understand the latest clinical developments and how to best apply that knowledge in clinical practice.

**BenEFITS OF ATTENDING**

- Learn about emerging treatments for the management of psychiatric disorders
- Hear about strategies for early diagnosis and intervention to improve outcomes
- Learn about how new therapies work to treat various psychiatric conditions
- Get a better understanding of the impact of psychiatric disorders for those affected
- Explore future directions for treating psychiatric disorders
- Earn CME credit while interacting with psychiatric experts and peers

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NEW

LOREEV XR™ (LORAZEPAM) IMPORTANT SAFETY INFORMATION

INDICATION FOR USE

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

CONTRAINDICATIONS

LOREEV XR is contraindicated in patients with:
• Hypersensitivity to benzodiazepines or any ingredients in LOREEV XR
• Acute narrow-angle glaucoma

Please see Important Safety Information continued on the back, and accompanying Full Prescribing Information, including BOXED WARNING, and Medication Guide.

Once-Daily Dosing
• 1 mg, 2 mg, 3 mg extended-release capsules
• Sprinkle dose option
• Dose in the mornings, with or without food

Pharmacokinetic Profile
• Slow plasma level rise (Tmax of 9 hours) at steady state
• Minimal fluctuations throughout the day
• Bioequivalent to lorazepam tablets dosed q8h at steady state1,2

Lorazepam Metabolism
• Not metabolized via the Cytochrome P450 isoenzyme pathway1,3
  — Metabolized via glucuronidation

Ensure patients have affordable access to LOREEV XR™ with the savings program

• Most retail pharmacies will automatically apply a copay savings program benefit
• Patients may download a copay card at loreevxr.com
• Covered patients pay as little as $20 per month
• Additional benefits available for uninsured patients and commercially insured patients whose insurance does not cover the product.

1 Individual costs may vary. Program eligibility and restrictions apply.

 Remember: 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.
IMPORTANT SAFETY INFORMATION (con’t)

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 lactase 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, see accompanying Full Prescribing Information with BOXED WARNING and Medication Guide.

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.