

# Psychiatric Times

Peer-Reviewed • Practice-Oriented

February 2021 • Vol. XXXVIII, No. 02

## Data-Driven

### How Technology Can Improve Psychiatric Practice

» Nidal Moukaddam, MD, PhD, and Ashutosh Sabharwal, PhD

As smartphone ownership has skyrocketed and internet connectivity has become a necessity, patients and clinicians alike have seen the potential of evidence-based digital interventions. However, mainstream clinical practice has been slow to adopt these new technologies. Reluctance to use digital interventions might be related to attitude/familiarity, knowledge, and systemic/liability concerns.

The slow adoption may also be due to a lack of interdisciplinary dialogue between app users (the consumer, the patient, the physician), app makers/designers (engineers, computer scientists, and artificial in-

telligence experts), and the clinical practitioners. Currently, app and wearables data do not directly correspond to psychiatric diagnoses. Incorporating technology into mental health treatment plans could allow clinicians to work smarter, with continuously updated information. Clinicians and patients would benefit greatly from novel clinical workflows that incorporate apps and wearables as long as they meet confidentiality/privacy requirements. Innumerable patients have phones and other digital devices that could

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## PSYCHIATRISTS ARE PHYSICIANS FIRST

### Never Forget the Fine Print: From Fertility Rites to “Miracle Med”

» Sharon Packer, MD

When the email from “Sam” arrived asking about adding a natural weight loss product

to his more mainstream prescription medications, I was not surprised. Binge eating was his *bête noire*. A onetime college athlete who lost his scholarship because of an ankle in-

jury, he had since sat around eating while watching sports on TV and lamenting his lost career. He desperately wanted to shed unwanted weight, but treatments that control bingeing do not guarantee weight loss. He had tried hoodia with no success. So, when he heard about a new natural weight loss concoction, he was understandably excited yet skeptical because he knew of the government’s crackdown on hoodia.

Sam forwarded me a laundry list of ingredients without hoodia but with yohimbine (*Pausinystalia yohimbe*).

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## FROM THE CHAIRMAN

# How Pharmaceutical Innovation Is Saving the World

In March 2020, the United States was in the early stages of the coronavirus disease 2019 (COVID-19) pandemic. The country shut down, and the economy ground to a halt to slow the spread of the virus. Think back to March and the uncertainties it held for us all.

Nine months later, the US Food and Drug Administration approved 2 COVID-19 vaccines under emergency authorization. Before New Year's Day, millions of Americans—including frontline physicians, health care providers, and our vulnerable populations in nursing homes—had received the vaccine.

Overall, the media has crafted a rather negative narrative about the COVID-19 pandemic. They described the US response to the pandemic as blundering from one mistake to the next.

Yet, a more accurate and underappreciated way to tell the story of the past 9 months revolves around heroism, innovation, and precise science, performed under unbelievable pressure.

**Let's not mince words: The United States and the world must appreciate the role of the pharmaceutical industry—the investigators, physicians, and business leaders—who are rescuing the world from COVID-19. It is the medical breakthrough of our lifetime. Consider these facts:**

- In this short time, scientists have identified a novel virus; unlocked and sequenced its genetic code; created new therapies to save lives; and developed multiple safe and effective vaccines using messenger RNA technology—a technology hopefully applicable to future vaccine development. Margaret Liu, MD, a biomedical scientist and member of the MJH Life Sciences™ COVID Coalition, called it a breakthrough for mRNA vaccines.

- The United States has 2 vaccines approved for emergency use: 1 from Pfizer/BioNTech and another from Moderna. Additionally, the AstraZeneca/Oxford vaccine is approved for emergency use in the UK. There are 64 additional vaccines currently undergoing clinical trials, including 20 in phase 3 trials. Worldwide, the pharmaceutical industry has answered the call and invested

heavily in this effort to prevent morbidity and mortality.

- This was the fastest vaccine development in history, and by a long shot. David Pride, MD, PhD, a microbiologist at the University of California, San Diego, estimates that vaccines typically take 10 to 15 years to develop. Until the COVID-19 pandemic, the fastest development timeline was 4 years, which was for the mumps vaccine.

- Many government systems moved to lessen the burden of onerous regulations and provided funding so vaccines could be developed quickly but with rigorous standards. Perhaps it should be a lesson that regulation and innovation can be calibrated more effectively during normal times as industry aims to develop new therapies for other diseases—cancer, diabetes, heart disease, and even psychiatric disorders.

Distribution of the vaccine, the next step in the process, will be as challenging as the development phase, if not more so. Again, the pharmaceutical industry is rising to the occasion, as factories worldwide are on overdrive to produce hundreds of millions of vaccine doses.



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## FROM THE EDITOR

# The 16-Minute Med Check

John J. Miller, MD | Editor in Chief

During the last year of my residency in psychiatry, I watched a TV series called *Northern Exposure*, a comedy-drama series that played for 6 years. Main character Joel Fleischman was a neurotic physician from New York City who had just completed his residency in family medicine. Joel had agreed to work for 4 years in Alaska in exchange for the state financing his medical education. He was assigned to work in the remote fictional village of Cicely, which had a lively and eccentric population.

One of my favorite scenes, which I can still vividly recall, was a conversation between Joel and Leonard, the local Inuit shaman. Leonard shares with Joel his wonder at the ways of modern medicine. He cannot understand how Joel can spend only 15 to 20 minutes with a patient and be able to construct a diagnosis and treatment plan from that brief encounter. Leonard explains to Joel that for him to diagnose and treat a patient he needs to live with that individual for several days to see what their stressors are, watch them while they sleep, understand their lifestyle and interpersonal interactions, and observe their diet patterns and exercise activity.

At that time, in 1990, insurance companies allowed us to meet with our patients for 1-hour visits each week. The first 10 minutes was usually focused on medication management, and the remaining 40 minutes were spent engaging in various types of psychotherapy. After my residency I practiced this style for a few years at a local community mental health center. Despite the weekly 50-minute appointments it often took me 6 to 12 months to begin to understand the complexities and biographical significances of each patient. I treated a man who presented with a classic major depressive disorder. He was a successful local businessman who rarely missed his weekly 50-minute appointment. It was only after meeting for 12 months that he started to discuss his chronic and disabling obsessive compulsive symptoms.



**DR MILLER** is medical director, Brain Health, Exeter, NH; editor in chief, *Psychiatric Times*™; staff psychiatrist, Seacoast Mental Health Center, Exeter, NH; consulting psychiatrist, Exeter Hospital, Exeter, NH; consulting psychiatrist, Insight Meditation Society, Barre, MA.

He felt shame and embarrassment when he first began to share his dark secrets, but ultimately had a great response to treatment.

It was in the early 1990s that the ensuing tragedy began. As managed care intruded into the medical profession, patients had to get authorization for their initial psychiatric evaluation and for 1 or 2 follow-up visits. I would then have to fill out a treatment plan form and request authorization for 3 or 4 more visits. After several years of this nuisance, the insurance plans determined they were spending more money to manage treatment authorizations than they were saving by managing us, so this protocol was discontinued.

The next step was a classic move-countermove battle of wits. Insurance companies decreased payments to psychiatrists for a 50-minute visit, because the insurance companies were of the opinion that lengthy visits could be provided by other professions who could be paid significantly less. As a result, psychiatric visits shrank to 30 minutes; payment for two 30-minute visits was significantly more than one 50-minute visit. The insurance companies executed their next

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countermove by lowering the payment amount for a 30-minute visit. A counter-countermove by some psychiatrists was to then see 3 patients per hour, allowing the billing for 3 units of treatment instead of 2. Alas, the response was a predictable counter-counter-countermove that ultimately led to the current general structure for psychiatrists to see patients for a so-called “15-minute medication check.”

Leonard the shaman would be extremely impressed or, more likely, appropriately deeply saddened by how little time psychiatric providers in most clinics now spend with patients. I would like to propose a new model: the 16-minute medication check.

**Think of all the additional information we could learn about or convey to our patients if we used that extra minute to simply ask 1 or more of these questions:**

1. Tell me about the most important individuals in your life.
2. What is it like for you in your work environment?
3. Do you have any questions about any of the medications that I am prescribing for you?
4. Have you considered a trial to lower one of your medication's dosage?
5. Could you remind me of your active medical problems?

6. What are your long-term goals in life?
7. Who lives with you, and how do you get along?
8. What are you most afraid of?
9. What is a typical breakfast, lunch, and dinner for you?
10. Do you feel rested when you wake up in the morning?
11. Who do you feel had the greatest influence on you growing up?
12. How do you express anger?
13. What do you do for relaxation?
14. Do you exercise regularly? If so, what type and how often?
15. Would you like me to review the common and rare side effects of your medications?
16. What is the one bad habit you would like to change?
17. When do you feel most at peace with yourself?
18. Do you feel safe in your home and your neighborhood?
19. How do you feel your treatment here is going?
20. Do you have any questions about your diagnosis(es)?

A final reflection: if you were meeting with a psychiatrist for a 15-minute medication check, how would you feel if you were asked any of these questions? Just asking! ☐

## From the Chairman

*Continued from Page 1*

Less than a month after the Pfizer vaccine was approved, more than 15.4 million doses of vaccine have been distributed throughout the country, and more than 4.6 million individuals have received their first dose, according to CDC data. Many patients are already receiving their second dose. All of this is incredible, considering 6 months ago many observers did not think a vaccine would be available until 2021.

Every day, more people will be vaccinated. After health care workers and our most vulnerable citizens, other frontline workers will be protected. Teachers will be vaccinated so our children can return to school. Soon, all Americans will be able to receive the vaccine at their doctor's office or at a CVS or Walgreens.

Remember, we accomplished this in only 9 months—with the help, dedication, and expertise of our pharmaceutical industry heroes. Next time you turn on the TV and see negativity, turn it off and imagine instead where we will be in 9 months. ☐

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# Data-Driven

Continued from Cover

be gathering relevant information, but the information present in those devices has no formal role in clinical practice yet.

## What Do Wearable Technologies Measure?

Wearables can include shirts, necklaces, headbands, wristbands, watches, shoes, and eyeglasses. They can be used to monitor physiological parameters such as temperature, heart rate, skin conductance, respiratory amplitude, and body movements, which may help monitor disease status.

Flexible biosensing is a rapidly growing industry and area of research. It aims to produce flexible material that can be worn as close to the skin as possible in a noninvasive and unobtrusive manner. These wearables can include physiological signal-monitoring sensors; customized designs with transmitters, receivers, filters, and circuit tracks—all with reduced size, lighter weight, and lower power consumption.<sup>1</sup> Biosensing can also be used to measure chemical levels in the body, such as blood sugar, calcium, lithium, and oxygen saturation.<sup>2</sup>

In the field of psychiatry, only the more basic sensing aspects are eyed as adjuncts for information-gathering and digital therapeutics. Yet, even in their most basic form, sensors have the possibility of changing the way psychiatrists monitor their patients' symptoms. Instead of relying on subjective information from patients, clinicians could gather objective data on sleep habits, activity levels, food intake, medication adherence, and even substance use. Onset of certain troubling patterns or departure from established baseline patterns serve as diagnostic cues. For instance, increases in motor activity (a proxy for agitation) can be a diagnostic prelude for mania.<sup>3</sup>

Key to success is the establish-

ment of a clear relationship between the objective measure and the disease or mental health issue. For instance, irregular respiratory amplitude might signal decompensation of asthma. Since the link between shortness of breath and an asthma attack is well understood, a wearable looking at such data could theoretically be implemented.<sup>4</sup> Turning to psychiatry, anxiety symptoms can occur in panic attacks and mimic asthma in an individual who has both disorders; in this case, irregular respiratory amplitude could signal worsening in either or both conditions. Interestingly, the wearable itself cannot make this determination and differentiate conditions unless an artificial intelligence algorithm gathers and interprets additional data points. A stepwise approach to this chain of events is portrayed in **Figure 1**.

## A Closer Look at Smartphone-Provided Information

The data gathered by smartphones are comparable to wearables, because most individuals carry smartphones on them most of the time. Information provided by a phone or a wearable is referred to as passive sensing, requiring no action on behalf of the user. Below is a non-exhaustive summary of phone-measured dimensions. Note that wearable bands used for fitness cover much of the same information but may not share all of it with users.

The most basic data a phone can provide is GPS information. GPS location tracking provides a detailed image of a patient's routine. Phones can also measure exposure to daylight, which can share information about the patients leaving their home. These 2 data points tell a story of isolation and psychomotor retardation, both potential indicators of worsening depression. Similarly, sleep fluctuations can be detected by examining screen on/off features and accelerometry data.

The use of text/SMS can establish an individual's sociability baseline. How large is a patient's social network? How many people do they interact with on a regular basis? How

long do their conversations last, and do they prefer phone to text? Deviations from this baseline can be seen in mood disorders (ie, isolation and withdrawal in depression; extraversion and increased sociability in mania); psychotic disorders (ie, isolation and withdrawal with worsening paranoia or persecutory delusions); and anxiety disorders and substance use disorders (ie, calls at erratic times; increased activity; certain suspicious locations). The length and content of verbal and written communication can also be indicative of pathology or relapses.

Lastly, movement anomalies and tremors can also be detected with smartphone-based monitoring and can be useful in assessing medication adherence and effectiveness.<sup>5</sup>

## Symptom Monitoring and Privacy and Confidentiality

The potential of technology to detect deviations in behavioral patterns is vast. However, privacy concerns are legitimate, and every effort needs to be made to protect individuals with mental illness, especially because they are a vulnerable population. For instance, could looking at interpersonal communications violate a patient's privacy and confidentiality? Linguistic analysis and natural language processing indicate high correlations between in-person clinical ratings and blinded ratings based on social media data posts,<sup>6</sup> as well as potential in discriminating unipolar from bipolar depression.<sup>7</sup> On Reddit, sentiment analysis, personal pronouns, and semantic category analysis differentiated belonging to a mental health support group versus other nonmental health groups.<sup>8</sup> Social media content has been looked at as a contender for collateral in mental health care.<sup>9</sup> Accessing content of social media posts could be valuable in assessing and following mood disorders.

Looking at an individual's conversations can be helpful in assessment and diagnosis of mood, psychotic disorders, and brain injuries, but carries risk of privacy invasion. Prosody assessment can help diagnose schizophrenia spectrum disorders by clarifying lexical and syntactic information.<sup>10</sup> With privacy-preserving measures and no content analysis, our group has proven that depressive symptom severity correlates with decreased text/SMS and call durations and frequency.<sup>11,12</sup> Privacy preserving analyses is more technically challenging, but may be more acceptable to patients in terms of sharing data and allowing speech recordings.

## Ecological Momentary Assessment

Ecological momentary assessment (EMA) refers to data reported by an individual in close temporal proximity to an event, which can help avoid recall bias. The use of smartphones has allowed EMA collection of feelings, reactions, and other behavioral measures more frequently than before. Answers in response to a prompt asking about mood are useful, especially in correlation with objective data from wearables or phones. In contrast to passive sensing, EMA cannot be collected continuously.

In the field of mental health, EMA is often centered on reports of mood but can also include questions about suicidality, self-harm impulses, hallucinations, substance or alcohol use, physical activity, self-esteem, etc. Both random and scheduled sampling are options, and the more frequent data collections allow for finer granularity in understanding microprocesses that govern emotional and behavioral experiences. EMA can also play a role in shaping emotions or behaviors by increasing awareness and, thus, needs to be studied carefully for potential placebo-like effect.<sup>13</sup>

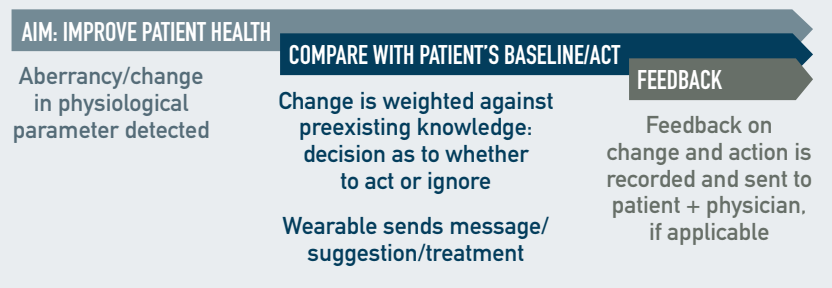
Choosing the right EMA is crucial to understanding the patient's experience, just as choosing the right interview question can facilitate therapeutic alliance. In selecting apps,<sup>14</sup> it is important to determine the goals. For example, would an event-contingent sampling (ie, asking a patient to log when they have cravings for a substance or urges to hurt themselves) be helpful? Is time-contingent sampling (ie, examining when things happen to rule out adverse effects or explore life occurrences on mood) a more appropriate option? EMA is also used to train artificial intelligence and deep learning algorithms to predict events, such as resurgence of auditory hallucinations or bad mood.<sup>15,16</sup> Once the algorithm is trained, frequent EMA is no longer needed.

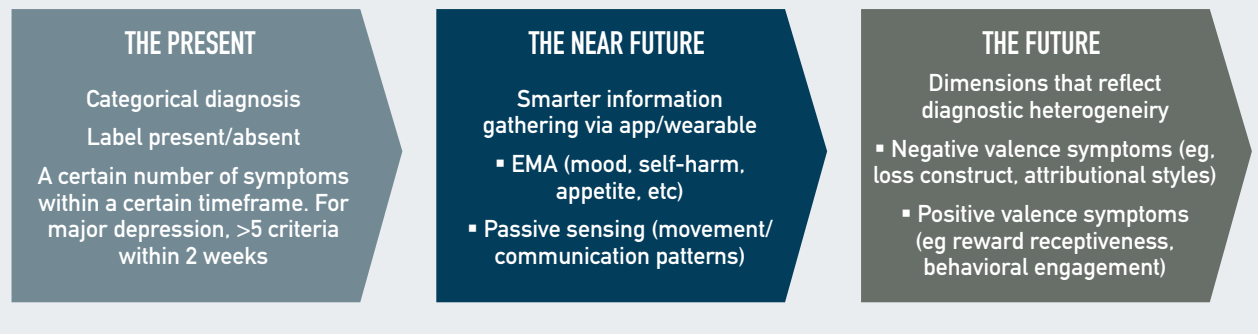
## Putting Technology Into Action

Referred to as digital health, the ability to leverage technology for encouraging positive behaviors is an area that could revolutionize health care, especially in psychiatry.

Mental disorders are heterogeneous. A divergence can exist between what a patient reports and what the psychiatrist sees (eg, mixed features in a manic episode). The following tips can help fit this phenomenology within EMA and passive sensing findings.

**Figure 1. Ideal Scheme of Detection and Change-Triggered Action From Wearables**



**Figure 2. Approaches in Psychiatry****Carefully evaluate prospective apps.**

The app evaluation model available on the American Psychiatric Association's website offers a helpful guide to clinicians wishing to evaluate such applications.<sup>17</sup> Specifically, clinicians should consider:

- On which platforms/operating systems does the app work? Does it work on a desktop computer?
- Has the app been updated in the past 180 days?
- Is there a transparent privacy policy that is clear and accessible before use? Does the patient understand it?
- Does the app collect, use, and/or transmit sensitive data? How are the data stored, and is storage claimed to be secure?
- Is there evidence of specific benefit from academic institutions, end-user feedback, or research studies? (Note: Most apps do not, hence the difficulty in recommending specific ones.)
- Does the app have a clinical/recovery foundation relevant to your intended use?
- Does the app seem easy to use? How much battery and data does it consume?
- Can data be easily shared and interpreted in a way that is consistent with the stated purpose of the app?

**Avoid making a diagnosis based on data points from an app.**

Psychiatric diagnosis is categorical and relies on specific symptoms for a predetermined duration as dictated by the DSM-5 or the International Classification of Diseases, Eleventh Edition. Wearables do not provide a diagnosis, but rather a set of data points. A symptom of depressed mood does not equate to major depression, nor does a hallucination equate to a formal thought disorder. In incorporating findings in your formulation, use the data as part of a full clinical picture. Discuss app findings with the patient while avoiding diagnostic labels.

**Think dimensional, not categorical.**

Symptom remission is the goal of treatment, but symptoms occur along a continuous spectrum. Findings from an app can be invaluable in helping patients move from partial to full remission. For instance, although a patient with depression may present with an improved affect and grooming suggestive of remission, the curves from a mood app show persisting poor functioning and, therefore, incomplete improvement. In this case, the improvement may have reached a certain threshold, which is not enough for full functional recovery. The dimension of depressed mood is distinct from the construct of a depressive disorder.

Apps and wearables generate an overwhelming amount of data that require specialized processing with deep learning algorithms. Clinicians should start with dimensions in which they have been trained, such as psychomotor retardation to agitation, depressed mood, food intake, and sleep. However, it is clear that other transdiagnostic dimensions can tell a lot about an individual's functioning, even if they are not part of traditional psychiatric diagnostic criteria. Functional imaging studies have largely moved in this transdiagnostic, dimensional direction, and these include psychological concepts such as impulsivity, compulsivity, sociability, and other biomarkers chosen based on functional connectivity and biomarker data.

**Figure 2** offers an example of dialogue between the categorical and dimensional approaches in psychiatry as mediated by wearable or app-provided information.

**Use data from apps in session to discuss progress with your patients.**

Data collected outside of appointments offer a glimpse into the patient's real life. In initiating use of any app or wearable, discuss the expectations and lay the foundation with the patient in terms of what the technology can do and cannot do. Then, during a later appointment,

ask the patient to show you their mood graphs, and use this information to initiate a dialogue on noted bad days, triggers, sleep pattern deviation, etc.

There is rapid turnover of apps and technology, with few applications withstanding the test of time. As such, it is difficult to recommend any particular application, but it is useful to know the main ones in the field. Examples include Daylio and T2 Mood Tracker for journaling; Woebot, CBT coach, and CBT-I Coach for cognitive behavioral basics and insomnia; and Calm and Youper for wellness. A clinician familiar with an app can better guide the conversation.

**Concluding Thoughts**

Technology can be useful as adjunct to information gathering, diagnostic clarification, symptom tracking, and teaching/reinforcing behaviors for patients with mental illness. Still in its infancy, this exciting field is rapidly growing and holding much promise.

**CASE VIGNETTE**

"Julie" is a young adult with depression. Pharmacological management has helped somewhat, but the patient reveals urges to self-harm and continued intermittent depressive symptoms. However, Julie is not fully open about this issue. Financial considerations and transportation issues preclude the addition of psychotherapy and more frequent visits. Interestingly, Julie wears a fitness band. At one of the appointments, you suggest looking at her sleep results and note a particular Thursday and Friday have a more interrupted pattern than other days. Upon closer inquiry, Julie reports alcohol bingeing on those days.

With this in mind, you suggest she install a cognitive behavioral therapy app for substance use (reSET, which is FDA-approved), and plan for closer follow-up visits.

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# Never Forget the Fine Print

Continued from Cover

Years had passed since I had seen that word in print.

“Was it safe?” was all he wanted to know. Whether it worked seemed to be a secondary concern. My short answer was no, and I promised a longer explanation at his next appointment. In the interim, flashbacks of another patient from long ago popped up. Although psychopharmacology has quickly evolved in the decades since the emergency department (ED) consult, that related case was too dramatic to forget.

I remember the frantic call from the ED staff, begging me to see their patient posthaste.

“Maybe you can prescribe lithium or haloperidol or something like that. We cannot contain him here, but we have nowhere to send him,” said the pressured voice on the phone. “He saw a psychiatrist, but that is all we know.”

It was Sunday midmorning, late summer, when many Manhattanites escape town leaving side streets empty and opening tables at New York City’s unending array of eateries. Uninterrupted by impatient New Yorkers demanding seats, out-of-towners could enjoy unhurried brunches, fussed over by glamorous waitstaff who were patiently anticipating their Broadway debuts. The tidy townhouses lined side by side behind the hospital conveyed an extra sense of calm that contrasted with rowdy Saturday nights.

Taking a shortcut, I quickly arrived at the ED, which was nearly abandoned. I peered through the window of the make-do quiet room and could see that the doctor who called the consult was not exaggerating. A tanned, middle-aged man stood a few feet behind the door. He looked to be 50-something, but he jumped and hopped like a child, in sync to the beat of an invisible drum. His thinning silver hair swung wildly. Most strikingly, his suit jacket was draped around his waist, hiding his backside and little else. Empty sleeves looped across the front, dangling like a loincloth, albeit one with a shiny—probably pricey—silk lining. Where he left his pants, shoes, socks, and shirt was anyone’s guess. All I knew is that he wore nothing else.

Per protocol, I checked the chart before walking into the room, not just for safety’s sake but to learn a little about the patient by skimming the demographics. He was, in fact, middle-aged, married, and, in hindsight, possibly a vestige of the *Mad Men* generation, although *Mad Men* had not aired yet. For that matter, sildenafil had not been invented, nor had the now-ubiquitous second-generation antipsychotics that are often used to treat bipolar disorder. Per the intake sheet, “Mr Smith” was a senior vice president at a name-brand advertising firm, even if his present posture suggested otherwise.

The history mentioned that his private psychiatrist, who had retreated to the Hamptons for the summer, referred all emergencies to the hospital, as per his answering machine message. Before leaving, said psychiatrist started him on lithium, then carbamazepine, maybe even valproate, but now everything spiraled out of control. Experience told me that advertising executives with bipolar disorder tendencies are not uncommon, because advertising takes high energy, unabashed enthusiasm, and lots of chutzpah, which

are abundant in hypomanic states. Yet it was also unlikely that someone with uncontrolled bipolar disorder could rise so high through the corporate ranks, even if his prescriptions screamed bipolar. It was also unlikely that this behavior represented garden-variety bipolar disorder, because the nurse noted that he was disoriented to time and place, distracted, and responding to unseen stimuli. His rapid, jerky movements put me on high alert for impending seizures, even though a cursory neurological exam had cleared him.

I scrolled through the medication list, checked the charted vital signs, scanned all labs listed, and looked for clues to explain this seemingly sudden deterioration. Even the toxicology screens were negative. The medications included several antihypertensives, which opened the possibility of a recent cerebrovascular accident secondary to hypertension, but he was moving all 4 limbs without restrictions, and his frenetic, dancelike activity functioned as a makeshift cardiac stress test, making it unlikely (but not impossible) that his strange symptoms followed hypoperfusion. There was only 1 odd entry, a little, nearly illegible word: *Yocon*.

In those days, we checked prescription pharmaceuticals through big, bulky *Physicians’ Desk Reference* editions with thin pages and small print. And that was where I found the culprit: that little word was the trade name for yohimbine, a reputed (but disputed) aphrodisiac used in fertility rituals in Cameroon, Central Africa, according to a memorable medical school ethnopharmacology lecture. I called the man’s internist, who had hospital privileges and even made rounds on weekends. The internist checked his chart and confirmed that a urologist had started the man on prescription yohimbine a few weeks earlier. The doctor noted that he added more antihypertensive medications soon after, which made sense, given that this herb can increase blood pressure and interfere with the efficacy of blood pressure medications.

The nurses crowded outside the room, eager for an explanation, and appreciative of the colorful story behind this mystery. Yohimbine was an  $\alpha_1$ -adrenergic agonist, a product of an East African tree with a similar name. It was marketed as an antidote to erectile dysfunction and subsequently approved for this purpose, despite equivocal evidence. Whether yohimbine helped in this regard was unclear, but its psychoactive properties were apparent. I wondered whether prescriptive yohimbine (or nonmedicinal yohimbe bark) directly increased libido as advertised, or whether it simply induced manic states in susceptible individuals, with the attendant hypersexuality of mania.

That theory was within the realm of possibility, especially because recent reports confirm that the stimulant especially affects individuals who are predisposed to bipolar disorder, as well as schizophrenia, panic disorder, and posttraumatic stress disorder. Even popular online consumer medical websites warn against its use in cases of depression because it can precipitate manic reactions.<sup>1</sup> The National Institute of Health’s National Center for Complementary and Alternative Medicine, now the National Center for Complementary and Integrative Health,

has since taken a harsher stance, warning against its use in individuals with any psychiatric history.<sup>2</sup>

Over time, we learned much about yohimbine and its positive and negative effects. Although it fell into disuse after the invention of the much more predictable PDE5 inhibitors indicated for erectile dysfunction, online marketers still promote it for a wide range of problems, including appetite suppression and obesity. Yohimbine gained greatest use as a veterinary antidote to animal tranquilizers. It has been misused by some humans, as was the case with ketamine, a onetime animal tranquilizer turned club drug that has recently been repurposed as a treatment for depression. No comparable success stories have been reported for yohimbine, although bodybuilders cite anecdotal evidence that the herb enhances exercise endurance. In contrast, forensic medicine journals report tragic deaths among young bodybuilders,<sup>3</sup> and note that yohimbine can cause delirium, hallucinosis, seizures, and sometimes deaths. An article in *American Journal of Psychiatry* confirms that it can switch depression into mania.<sup>1</sup>

**“There was only 1 odd entry, a little, nearly illegible word: *Yocon*.”**

Importantly, dangerous interactions can occur with phenothiazines—so it was fortunate that the patient quieted down with a dark, soundless room and intravenous diazepam, prescribed by the neurologist to stop seizures should they occur. Aided by the tincture of time, and a short stay upstairs once a bed opened, he reportedly returned to baseline. When I checked on him a few days later, he did not recall this episode.

In hindsight, our mystery man escaped easily. Who knows what tragedies could have occurred had strong psychotropics been added to his medication mix without stopping the clandestine culprit? At worst, lethal medication interactions could have followed. And, at best, he would have been condemned to a lifetime’s treatment for a condition that might not have emerged without this botanical boost.

Fortunately, psychiatrists are physicians first, and we must consider the big picture, without reflexive and thoughtless prescriptions for psychotropics—even if the general public, as well as other medical professionals, assume that is all we do. As for Sam, I expect him to appreciate this warning story about yohimbine, even if the negative studies about its efficacy for weight loss disappoint him.

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# PSYCHOCARDIOLOGY

## Exploring Integrated and Collaborative Care

### » Michelle Riba, MD, MS

The past 20 years have seen a burgeoning interest in the interface between psychiatry and cardiology—psychocardiology. More fellows are seeking training in this subspecialty. Increasing numbers of consultation-liaison faculty are finding careers in working collaboratively with colleagues in cardiology, cardiac surgery, cardiac transplantation, psychology, nursing, social work, pharmacy, and many other disciplines. It has been exciting to see the development of guidelines and pathways to provide integrated and collaborative psychocardiology care in areas such as heart failure, pulmonary artery hypertension, arrhythmias, vascular diseases, and myocardial infarction and to seek earlier intervention that can make sustained behavioral changes and prevent disease, such as in diet, exercise, nicotine use, substance use, stress modification, sleep, etc.

We are seeing these changes in patients across the life cycle. Our colleagues in other medical disciplines are trying to understand and frame this goal from the lens of a public health mandate because depression, cardiovascular diseases, and diabetes are leading causes for global health disabilities.<sup>1</sup> At the Academy of Consultation-Liaison Psychiatry, special interest groups in psychocardiology have been well attended, and there are more sessions on psychocardiology topics at our annual meetings and articles in the prestigious journal *Psychosomatics*.

In 2012, I coedited the book *Psychiatry and Heart Disease: The Mind, Brain and Heart*. Lawson Wulsin,

MD, wrote: “The current need... follows from the profusion of research... showing how the cardiovascular system and psychological distress are each intimately linked to the central, peripheral, and autonomic nervous systems, the immune system, and limbic-hypothalamic-pituitary-adrenal-gonadotropic axis.”<sup>2</sup> One only has to look at the significance and severity of coronavirus disease 2019 on the cardiovascular system and on mental health to appreciate the relevance of psychocardiology.

**One only has to look at the significance and severity of coronavirus disease 2019 on the cardiovascular system and on mental health to appreciate the relevance of psychocardiology.**

Many topics fall within the psychocardiology domain. For this Special Report, we have chosen a few of the many important topics and issues, with key leaders presenting information in clinically useful and helpful ways. Understanding the underlying mechanisms of and developing effective treatments/interventions for the cardiovascular system as it relates to psychosocial distress and the nervous system in a bidirectional manner are key.

My sincere appreciation to our wonderful contributors of this special series.

*Dr Riba is professor in the Department of Psychiatry and director of the Consultation-Liaison Psychiatry fellowship at the University of Michigan in Ann Arbor; she also is deputy editor in chief emeritus of Psychiatric Times™.*

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# Positivism and Heart Health: Issues for Psychiatrists

» Christopher M. Celano, MD, and Jeff C. Huffman, MD

When considering the relationship between mental and cardiovascular health, most conversations focus on negative emotions and related disorders, such as depression. This is not surprising, given that depression is common and associated with the development and progression of cardiovascular disease.<sup>1</sup> This relationship is so strong that the American Heart Association considers it to be a risk factor for poor outcomes after a myocardial infarction,<sup>2</sup> and this relationship has been the basis for depression treatment programs for patients with heart disease.

Although identifying and managing depression in patients with heart disease is important, focusing solely on negative psychological constructs has a downside. Since major depressive disorder affects only approximately 15% of patients with heart disease,<sup>1</sup> depression treatments are applicable only to those 15% of individuals who suffer from that psychiatric illness. This raises the question of whether there are ways for psychiatrists to help all cardiac patients—not just those with depression or anxiety—feel better both emotionally and physically.

Research into well-being and related constructs may provide an answer. In the past 10 to 15 years, researchers have begun to identify relationships between well-being constructs (eg, optimism, positive affect) and cardiovascular health. In individuals without heart disease, these constructs are associated with a reduced risk of heart disease and all-cause and cardiovascular mortality.<sup>3,4</sup> Among those with established heart disease, well-being constructs reduce one's risk for major adverse cardiac events and mortality.<sup>3</sup> Importantly, these relationships are independent of medical comorbidities, sociodemographic factors, and—oftentimes—depression.<sup>3</sup>

## Well-Being and Heart Health

Both biological and behavioral mechanisms may explain the relationship between well-being and cardiovascular health. Positive psychological constructs are linked with physiologic processes that have been implicated in heart disease. This includes better autonomic functioning (ie, reduced sympathetic activation and increased parasympathetic activation), lower levels of inflammation, improved endothelial function, and lower levels of cortisol in some, but not all studies.<sup>3</sup> There is even greater evidence for the relationships between well-being constructs and cardiovascular health behaviors. Positive constructs are prospectively and independently associated with more physical activity, a healthy diet (eg, more fruits and vegetables), medication adherence, engagement in treatment programs that promote cardiac recovery (eg, cardiac rehabilitation), and smoking cessation.<sup>3</sup>

## Can Well-Being Be Cultivated?

Recent research suggests that well-being may be

enhanced through interventions that focus on the reduction of stress, enhancement of calmness or relaxation, and promotion of positive psychological constructs. Meditation, mindfulness training, yoga, tai chi, and other integrative therapies can induce states of relaxation and calmness and can be incorporated into daily life. These types of interventions appear to be effective at reducing stress, depression, and anxiety in patients with vascular disease (including cardiovascular disease) or heart failure.<sup>5,6</sup> Some studies have found these interventions also improve exercise capacity<sup>7</sup> and downstream cardiovascular outcomes, such as hospitalizations.<sup>6</sup>

Positive psychology interventions, which emphasize the systematic completion of activities to cultivate positive psychological constructs, have become increasingly popular.<sup>8</sup> These activities are simple to perform and may include writing a letter of gratitude, using a strength in a new way, or imagining a best possible future for oneself. These interventions have been studied in thousands of individuals and consistently improve well-being and reduce depression.<sup>9</sup> Some interventions also have been shown to improve cardiac health behaviors, such as physical activity and medication adherence,<sup>10,11</sup> when delivered alone or in combination with health behavior change interventions (eg, motivational interviewing). There have been preliminary positive results for in pilot trials for acute coronary syndrome,<sup>12</sup> heart failure,<sup>13</sup> type 2 diabetes,<sup>14</sup> and other cardiac-related conditions.

Although randomized trials for integrative and positive psychology interventions are needed, promoting well-being in individuals with heart disease (and, really, in anyone) makes intuitive sense. Many of the positive constructs—such as mindfulness, relaxation, optimism, gratitude, kindness, life

purpose—that these interventions aim to cultivate are things that anyone would benefit from experiencing more frequently. These interventions provide a system or framework to change one's mindset from focusing on negative things in our lives to savoring and enhancing the positive experiences we have and setting ourselves up for more.

## Cultivating Well-Being

Psychiatrists are well positioned to help all patients cultivate well-being. For example, if asked to consult on a patient with significant anxiety following a cardiac event, psychiatrists can teach the patient to use mindfulness (eg, relaxation response training, guided visualization). A patient with heart failure who is demoralized due to the severity of their symptoms can be encouraged to focus on those tasks they can still perform and have meaning to shift their focus positively. Finally, individuals who are recovering from cardiac events who are struggling to increase health behaviors can benefit from focusing on positive future outcomes and the use of strengths to reach their health behavior goals. The goal is to help patients reduce stress, use their strengths to approach challenges, and recognize positive events that are happening around them.

## Preventing Burnout

Well-being is important not only for patients but also for physicians, who frequently work under stressful conditions and experience high levels of burnout. Fortunately, there are many simple ways to promote well-being (Table 1). This could include setting aside time to engage in an enjoyable or meaningful activity, making a point to discuss a positive event with a family member or friend, thinking about one aspect of the day for which you are grateful before going to bed, or using the strength of perseverance to work toward a life goal. It could also involve incorporating meditation or prayer into routines, or setting aside time for health behavior activities, such as exercise. Although many of these things seem simple, they are easily overlooked, and engaging in them

Table 1. Activities To Promote Well-Being

Target construct	Activities
Gratitude	<ul style="list-style-type: none"> <li>■ Cultivate awareness of positive events by writing about them in a journal.</li> <li>■ Capitalize on positive events by discussing them with family members or friends.</li> <li>■ Express gratitude to others by sending them a thank you note.</li> </ul>
Strengths/resources	<ul style="list-style-type: none"> <li>■ When faced with a challenge, think about how you approached similar challenges in the past successfully.</li> <li>■ Use perseverance to reach a goal in your life.</li> <li>■ Reach out to a friend you haven't spoken to in some time to catch up with them.</li> </ul>
Enjoyment	<ul style="list-style-type: none"> <li>■ Schedule 15 minutes into your day to read a book or engage in another enjoyable activity.</li> <li>■ Find an online activity (eg, a trivia night, watching a movie) that you can do with a friend.</li> </ul>
Meaning	<ul style="list-style-type: none"> <li>■ Engage in a creative activity (eg, woodworking, photography) that brings you a sense of meaning.</li> <li>■ Think about what is most important in your life. Then, consider ways to spend more of your time focusing on those things that are important to you.</li> <li>■ Perform an act of kindness for someone in your community.</li> </ul>
Calmness	<ul style="list-style-type: none"> <li>■ Perform breathing exercises to induce a state of calmness.</li> <li>■ Induce the relaxation response using a CD or audio file.</li> </ul>

**Table 2.** Resources to Promote Well-Being, Reduce Stress, and Build Resilience

Type	Resource	Description
Websites	www.mindful.org	Provides free resources including an overview of meditation, guided meditations, and educational information
	www.thewellnesssociety.org	Provides an overview of mindfulness and meditation resources, with links to books, podcasts, and courses
	www.ppc.sas.upenn.edu	University of Pennsylvania's Positive Psychology Center contains links to books, websites, and other positive psychology-related resources.
	www.hsph.harvard.edu/health-happiness	Lee Kum Sheung Center for Health and Happiness at the Harvard School of Public Health contains educational, research, and training information for professionals, as well as links to resources.
	www.heart.org	American Heart Association (click on "Healthy Living") shares important information about diet, physical activity, and lifestyle changes—including stress reduction techniques.
Mobile applications	Insight Timer (www.insighttimer.com)	Mobile app that provides free guided meditations, yoga videos, and resources to improve sleep
	Headspace, Breethe	Mobile apps that provide meditations, stress reduction techniques, and other resources; paid subscription required
Podcasts	The Happiness Lab (www.happinesslab.fm)	Podcast that provides information about recently performed research in positive psychology, well-being, and related areas
	Mindful in Minutes (www.mindfulinminutespod.com/listen)	Podcast that provides a series of guided meditations

regularly can help you develop habits that can have mental and physical health benefits.

Many free or inexpensive resources related to positive psychology, mindfulness, meditation, yoga, etc, can be found online. **Table 2** contains a sample of the websites, podcasts, and mobile applications to help begin this positive journey. Although the number of available resources can seem overwhelming, it can be helpful to try a few different resources to see which ones work best.

### Concluding Thoughts

Well-being and its related constructs are increas-

ingly identified as being important components of cardiovascular health. Cultivating positive psychological constructs is possible through simple-to-perform exercises, and psychiatrists are in a unique position to help patients with and without heart disease feel more positive and hopeful. This, in turn, can have substantial effects not just on mental health, but on health behaviors and downstream physical health outcomes as well.

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## The ABCs of Cardiac Screening and Electrocardiography

» Margo C. Funk, MD, MA, and Theodore A. Stern, MD

Psychiatrists prescribe many medications that are associated with cardiovascular risks, and they treat many individuals who have cardiovascular disease and take cardioactive agents. Unfortunately, adverse cardiac effects of psychotropics are wide ranging. They include electrical abnormalities (eg, conduction system abnormalities, tachyarrhythmias, and sudden cardiac death) and structural abnormalities (eg, ischemia, myocarditis, and heart failure).

The 12-lead electrocardiogram (ECG) is a com-

mon method for assessing functional and structural heart disease. Given the prevalence of cardiac disease and the frequency with which psychotropics can create cardiac adverse effects, psychiatrists should be proficient in the safe administration of medications that require ECG screening. Safe psychiatric practice dictates that a comprehensive personal and family history of cardiovascular disease is obtained before psychotropics are prescribed.

Psychiatrists should be able to recognize components of the ECG, measure specific intervals between waveforms (such as the QT interval), and decide whether (and for whom) medications are safe. Lastly, psychiatrists should understand the

electrophysiologic effects of certain psychotropics so they can make informed decisions based upon the ECG findings, including dose adjustments, medication discontinuation, or referral for cardiology consultation.

When prescribing many common medications, clinicians should consider an ECG, along with the following questions: When should I order an ECG before starting a patient on a psychotropic medication? What categories of cardiac effects are associated with which medication classes? What electrophysiologic abnormalities should be identified on the ECG? Which ECG abnormalities make prescribing certain psychotropic medications problematic (**Table**)?

### Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) are sodium channel blockers with cardiac effects that closely resemble those of other class I antiarrhythmic medications.

**Table.** The Impact of Psychotropics on Cardiac Function and the Electrocardiogram

Drug	Cardiac adverse effects	Baseline ECG	ECG and other monitoring <sup>a</sup>	ECG pathologies of concern	Contraindications
TCAs	Tachycardia, orthostatic hypotension, AV block, VCD, complete heart block, hypertension, MI, SCD	Strongly recommended, especially when aged ≥ 40 yrs	Regular monitoring in older adults, including ECG and BP	Prolonged PR interval, bundle branch block, Q-waves (remote ischemia), QTc prolongation	<ul style="list-style-type: none"> <li>■ Ventricular conduction delay (QRS ≥ 110 ms)</li> <li>■ Ischemic heart disease (coronary artery disease, prior MI, post-PCI, post-CABG)</li> </ul>
Stimulants	Tachycardia, hypertension, MI, stroke, SCD	<ul style="list-style-type: none"> <li>■ Children: reasonable to obtain but not mandatory</li> <li>■ Young to middle-aged adults: obtain if available</li> <li>■ Adults ≥ aged 55 yrs: recommended</li> </ul>	Monitor HR and BP at least 2x/yr	Any ECG abnormalities or change from baseline	Structural cardiac abnormalities, cardiomyopathy, heart rhythm abnormalities, coronary artery disease, or other serious heart problems
Clozapine	<ul style="list-style-type: none"> <li>■ CAM (dyspnea, palpitations, tachycardia, low to moderate fever, flu-like illness, nausea, dizziness, occasional chest pain)</li> <li>■ CAC (dyspnea, tachycardia, palpitations, chest pain, fatigue)</li> <li>■ SCAC (typically asymptomatic)</li> </ul>	<ul style="list-style-type: none"> <li>■ Consider obtaining a baseline ECG as a comparator if concerning symptoms for CAM arise</li> <li>■ Must be balanced with available resources</li> </ul>	<ul style="list-style-type: none"> <li>■ Consider weekly ECG, troponins, CRP, vital signs (including temperature) for first 4 wks of treatment</li> <li>■ Obtain a new ECG, cardiac enzymes (CAM), and echocardiography if concerns arise for CAM/CAC/SCAC</li> </ul>	ST segment depression > 1 mm or T-wave inversion in ≥ 2 contiguous leads other than aVR	No absolute contraindications; most cases of CAM/CAC occur in patients without cardiac disease
QTc-prolonging drugs <sup>a</sup>	TdP (lightheadedness, dizziness, syncope, seizure-like episode, SCD)	Variable	Variable	QTc/JTc prolongation, pathologic U waves/T2 waves/notched T waves, bradycardia	No absolute contraindications; requires a comprehensive risk-benefit analysis; most cases of TdP occur with QTc > 500 ms

<sup>a</sup>Obtain a comprehensive personal and family history of cardiac disease prior to medication initiation.

TCAs primarily delay cardiac conduction (through the His bundle), increase heart rate (via anticholinergic adverse effects), and cause orthostatic hypotension (via alpha blockade). Adverse cardiovascular events may also include hypertension, myocardial infarction (MI), and stroke. In healthy adults, TCAs typically lack significant cardiac effects when taken as prescribed. However, TCAs should be avoided in individuals with preexisting ventricular conduction delay ([VCD], most commonly a bundle branch block), Brugada syndrome, or ischemic heart disease (coronary artery disease including MI, history of percutaneous coronary intervention, or coronary artery bypass grafting), as TCAs confer an increased risk of symptomatic rhythm disturbances, mortality, and sudden cardiac death.<sup>1-3</sup> Use of TCAs in the period following acute MI is contraindicated by the US Food and Drug Administration (FDA).<sup>1</sup>

Although no guidelines exist for using electrocardiographic screening and monitoring when prescribing TCAs, it is standard practice to obtain an ECG before prescribing a TCA to rule out unrecognized VCD or ischemic heart disease, especially in individuals aged 40 or older.<sup>4</sup> Older adults who are prescribed a TCA should undergo cardiac and blood pressure monitoring on a regular basis.<sup>1</sup>

### Stimulants

Stimulant medications are sympathomimetic amines that increase resting heart rate and systolic blood pressure. Cases of sudden death, MI, and stroke have been reported in both children and adults with concurrent use of stimulants.<sup>5</sup> Package insert labeling on all stimulants warns of serious cardiovascular events in children, adolescents, and

adults with structural cardiac abnormalities, cardiomyopathy, heart rhythm abnormalities, coronary artery disease, or other serious heart problems.<sup>6</sup> All patients being considered for treatment with a stimulant should have a personal and family cardiac history collected and a physical exam performed. Screening positive for any cardiac issues requires further evaluation by cardiology, which may well include an ECG and echocardiogram.

Baseline ECG screening by psychiatrists for patients without a history of cardiac disease is controversial, especially in children. In 2008 the American Heart Association (AHA) recommended obtaining an ECG for all children before initiating treatment with a stimulant or atomoxetine. Later that year, the American Academy of Pediatrics (AAP) recommended against obtaining a baseline ECG, citing concern that the requirement for ECG screening may be a prohibitive public health barrier.<sup>7,8</sup> Following these divergent recommendations, a joint statement by the AHA and AAP later that year advised that ECG screening in the absence of known cardiac disease is optional and should be based on the physician's judgment. The joint statement was later revised to read that it is reasonable to obtain a pretreatment ECG.<sup>9</sup>

In a large 2011 study of children and young to middle-aged adults on medications for attention-deficit/hyperactivity disorder, researchers did not find an association between current stimulant use and an increased risk for serious cardiovascular events.<sup>10,11</sup> The data remained mixed across age groups; in adults 55 years or older, use of stimulants may worsen existing cardiac disorders. All patients treated with stimulants should have their heart rate (HR) and blood pressure (BP) monitored

regularly. For children and young to middle-aged adults, it is reasonable to obtain a screening ECG (if available) before initiating treatment. For geriatric patients, a pretreatment ECG with twice-yearly HR and BP monitoring is recommended.<sup>12</sup>

### Clozapine

Psychiatrists are typically trained to obtain an ECG before starting clozapine because of the risk of death associated with clozapine-associated myocarditis, clozapine-associated cardiomyopathy, and subclinical clozapine-associated cardiotoxicity.<sup>13</sup> Clozapine-associated myocarditis is an inflammation of the myocardium; its etiology is unclear but may be due to a type 1, immunoglobulin E-mediated acute hypersensitivity reaction to clozapine.<sup>14</sup> Clozapine-associated myocarditis is best diagnosed through detection of clinical signs and symptoms, ECG changes, abnormal cardiac biomarkers, and results of cardiac imaging (eg, echocardiography and cardiac magnetic resonance imaging).

An endomyocardial biopsy remains the gold standard for diagnosing myocarditis; since it is an invasive procedure, its use is limited due to the inherent risk of complications. Clozapine-associated cardiotoxicity is a disorder of dysfunctional myocardial contractility that results in a reduced left-ventricular ejection fraction (EF). The diagnosis of clozapine-associated cardiotoxicity is supported by a reduced EF (< 50%) and an increased B-type natriuretic peptide (BNP).<sup>15</sup> Subclinical clozapine-associated cardiotoxicity is typically asymptomatic; however, it includes paroxysmal atrial fibrillation and mild left ventricular/biventricular functional impairment. Echocardiography and elevation of N-terminal pro-BNP are helpful in the diagnosis of subclinical

clozapine-associated cardiotoxicity.<sup>13</sup>

Most cases of clozapine-associated myocarditis, clozapine-associated cardiotoxicity, and subclinical clozapine-associated cardiotoxicity occur in patients without cardiac disease or other medical risk factors. In these cases, the utility of obtaining a baseline electrocardiography is controversial. An ECG is not required before initiating clozapine. Ordering an ECG must be balanced against the availability of resources in treatment settings, which may not have ready access to electrocardiography.<sup>15,16</sup> Clear protocols for monitoring myocarditis and cardiomyopathy in patients treated with clozapine patients are lacking.<sup>13</sup>

Several studies have demonstrated that most cases of myocarditis occur in the first 4 weeks of treatment. Consequently, some investigators have suggested that levels of troponins and C-reactive protein should be obtained, and ECGs should be monitored at baseline and weekly for the first 4 weeks (being mindful of > 1 mm ST segment depression or T-wave inversion in 2 or more contiguous leads, other than lead aVR).<sup>17,18</sup> Other investigators have suggested that ECG monitoring should be completed only if symptoms arise that are concerning for myocarditis (eg, dyspnea, palpitations, tachycardia, mild or moderate fever, influenza-like symptoms, nausea, dizziness, and chest discomfort) or cardiomyopathy (eg, dyspnea, tachycardia, palpitations, chest pain, and fatigue) or if a patient presents to the hospital for a medical concern.<sup>13,15,16</sup>

When resources allow, clinicians should consider a conservative approach to clozapine and should obtain a baseline ECG and a weekly ECG in addition to laboratory monitoring during the first 4 weeks of treatment. However, this conservative approach should not preclude treatment when it is outweighed by the risk of psychiatric morbidity in a high-risk psychiatric population.

### QTc-Prolonging Psychotropics

Psychiatrists routinely prescribe psychotropic medications that prolong cardiac repolarization, thereby increasing the risk for torsades de pointes (TdP), a potentially fatal cardiac arrhythmia. The corrected QT (QTc) interval on the ECG is the most widely accepted indicator of TdP risk and a major drug-safety benchmark.

In 2020, the American Psychiatric Association (APA) Council on Consultation-Liaison Psychiatry and the American College of Cardiology (ACC) published an official action paper, “QTc Prolongation and Psychotropic Medications.”<sup>19</sup> This expert work group developed clinical guidelines for practicing psychiatrists. The guidelines addressed cardiovascular risk and monitoring for psychotropics that could increase the risk of TdP. One of the most important considerations was that there was no absolute maximum QTc level at which a QTc-prolonging medication should not be prescribed.

Most cases of TdP occur when the QTc is greater than 500 milliseconds. This is routinely used as a cutoff point, above which the risk of cardiac complications substantially increases, even in the absence of other risk factors. Physicians must perform a comprehensive risk-benefit analysis, weighing the cardiac risk of prescribing a drug against the risk of psychiatric destabilization if the drug is not prescribed. Physicians must also con-

sider other risk-mitigation strategies and request consultation from other specialties as applicable. When prescribing a medication that may prolong the QTc interval, recommendations for obtaining a baseline ECG as a screening test are highly variable and dependent on use of other drugs. (For a detailed assessment of QTc prolongation and risk of TdP, please see “Understanding the QTc: Issues for Psychiatrists” online.)

### ECG Interpretation

It is critical for psychiatrists to establish adequate knowledge of and comfort with electrocardiographic abnormalities, such as QTc prolongation. Psychiatrists must learn to recognize when other abnormalities, like VCD or remote ischemia, should preclude prescription of a psychotropic medication. Psychiatrists should, and will, be looked on as complex psychopharmacology experts and must be comfortable understanding associated levels of cardiac risk.

Regarding the role of psychiatrists in ECG interpretation, 2 additional themes emerged from the 2020 APA action paper on QTc prolongation. First, there was an expectation that basic ECG interpretation is within the scope of a psychiatrist. A 2001 clinical competence statement on electrocardiography by the ACC and AHA recognized that physicians who are not formally trained in ECG interpretation may provide preliminary interpretations, especially in time-sensitive clinical scenarios or in the absence of a formally trained ECG interpreter.<sup>20</sup>

The second theme suggested that we should support, educate, and empower psychiatrists to develop competence in ECG interpretation. The ACC/AHA competence statement advised that physicians of any specialty whose interpretations contribute to clinical decision-making should be able to “define, recognize, and understand the basic pathophysiology of certain electrocardiographic abnormalities.”<sup>20</sup> Unfortunately, psychiatrist competency and comfort with ECGs vary significantly, especially beyond the practice of consultation-liaison psychiatry and tertiary hospital settings. The training of psychiatrists in ECG interpretation represents a unique and much-needed opportunity for future program and curricular development.

### Concluding Thoughts

It is essential for psychiatrists to be knowledgeable about the cardiac effects of psychotropic medications and to know when to consider pretreatment ECG screening. When prescribing TCAs, stimulants, clozapine, and high-risk QTc-prolonging medications, psychiatrists must perform a thorough personal and family history of cardiac disease and obtain an ECG or cardiology consultation when indicated. Premorbid cardiac conditions, specifically VCD, ischemic heart disease, and risk factors for TdP including concurrent QT-prolonging medications, electrolyte disturbance and bradycardia should prompt increased vigilance.

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# Opportunities in Managing Treatment-Resistant Depression and Tardive Dyskinesia

CONTINUING MEDICAL EDUCATION

follow-up from the  
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Upon successful completion of this activity, you should be better prepared to:

- Describe current strategies and recent advances in treating treatment-resistant depression
- Explain the mechanism of action of therapeutic agents used to treat tardive dyskinesia

Treatment-resistant depression (TRD) and tardive dyskinesia are common conditions in psychiatry that present challenges in management, and in some cases may be related. Recent US Food and Drug Administration (FDA) approvals of therapies and advances in understanding these conditions provide new opportunities for improved outcomes.

## Recent Additions to Treatment-Resistant Depression Options

Up to 1 in 5 American adults are estimated to meet the criteria for major depressive disorder (MDD) during their lives, and approximately 30% of individuals with MDD are resistant to conventional therapies.<sup>1,2</sup> Although a number of definitions have been proposed for TRD, a common description is 2 or more unsuccessful trials of antidepressant agents with appropriate dosage and duration.

Guidelines from the Canadian Network for Mood and Anxiety Treatments provide an approach to patients with TRD.<sup>3</sup> For patients with inadequate response to a first-line antidepressant, factors that support switching to another antidepressant include poorly tolerated side effects or less than 25% improvement with the initial treatment, patient preference, and reduced urgency to achieve a response (such as less severe symptoms or functional impairment).

Considerations that support adding an adjunctive therapy include a history of 2 or more antidepressant trials, good tolerance and at least 25% improvement with the initial antidepressant, and greater urgency to achieve a response.<sup>3</sup> The guidelines suggest considering psychotherapy and neurostimulation in patients with an inadequate antidepressant response.

## Therapies that may provide additional options for patients with TRD include the following:

**ESKETAMINE NASAL SPRAY.** In 2019, this ketamine enantiomer became the first FDA-approved therapy for TRD that targets the glutamatergic system.<sup>4</sup> The therapy is approved for adults taking an oral antidepressant, and each 2-spray device contains 28 mg of esketamine.<sup>5</sup> It is only available through a Risk Evaluation and Mitigation Strategy (REMS) program and bears a black box warning for seda-

tion, dissociation, risk of suicidal thoughts and behaviors, and potential for abuse and misuse. Patients must self-administer the treatment under the supervision of a health care provider and remain for monitoring for at least 2 hours. One adverse event that is important to identify during monitoring is increased blood pressure.<sup>4,5</sup>

**INTERMITTENT THETA BURST STIMULATION (iTBS).** Approved by the FDA in 2018 for treating adults with TRD, iTBS provides 600 pulses of theta burst stimulation in 3 minutes, which are intended to mimic natural theta rhythms that are associated with the improved induction of synaptic long-term potentiation.<sup>6,7</sup> The therapy demonstrated noninferiority to repetitive transcranial magnetic stimulation, delivered in 37.5-minute sessions, in 414 adults with nonresponse to an antidepressant or inability to tolerate at least 2 trials of antidepressants. The primary outcome was reduction in Hamilton Depression Rating Scale-17 score. The most common adverse events in the iTBS group were headache, fatigue, and dizziness, with a similar number of serious adverse events in both groups.<sup>7</sup>

## VMAT2 Inhibitors for Tardive Dyskinesia

Tardive dyskinesia (TD) is a concern with nearly all dopamine receptor blocking agents (DRBAs), with the possible exception of clozapine.<sup>8</sup> Though newer antipsychotics have a lower likelihood of causing TD, they are still associated with risk. A meta-analysis of randomized controlled trials comparing antipsychotic therapies used for at least 3 months found an annualized TD incidence of 6.5% with first-generation antipsychotics versus 2.6% with second-generation agents.<sup>9</sup> Given the growing use of these drugs, the number of individuals at risk of TD may be rising.<sup>8,10</sup>

The availability of the following vesicular monoamine transporter type 2 (VMAT2) inhibitors has provided new options for improving the quality of life in patients with TD; these work by reducing the presynaptic storage and release of dopamine, without the impact of nonselective VMAT inhibition such as the bronchospasm, nausea, and hypotension that can occur with reserpine.<sup>8,10</sup>

In 2017, the FDA approved deutetrabenazine, a longer-acting version of tetrabenazine, for the treatment of TD in adults. The approval was based on the results of phase 3 studies in which most patients continued to take antipsychotic medication.<sup>8,11</sup> Patients showed significantly greater improvement in Abnormal Involuntary Movement Scale (AIMS) score versus placebo. The most common adverse reactions in clinical trials were nasopharyngitis and insomnia.<sup>11</sup>

The agency also granted approval to valbenazine in 2017 for treating adults with TD.<sup>8</sup> The drug was associated with significantly improved AIMS

scores compared with placebo in patients who were typically continuing to use DRBAs. It is taken as a once-daily dose, and the most common adverse reaction in clinical trials was somnolence.<sup>12</sup>

In its new practice guidelines for schizophrenia, the American Psychiatric Association recommended that patients with moderate to disabling TD associated with antipsychotic therapy receive VMAT2 inhibitor treatment, preferably deutetrabenazine or valbenazine over tetrabenazine.<sup>13</sup>

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## BIPOLAR UPDATE

# COVID-19 Pandemic's Effects on Assessment & Psychopharmacological Management

» David N. Osser, MD

Literature is emerging on the effects of the coronavirus disease 2019 (COVID-19) pandemic on patients with bipolar disorder. This is part of the much larger literature on assessment and management of mental disorders during the pandemic.<sup>1</sup>

Our group of 11 clinicians at the US Department of Veterans Affairs Bipolar Disorders Telehealth Program recently published a summary of lessons learned from using telehealth modalities (videoconferencing and telephone contact) with more than 3000 veterans whose caregivers submitted consultation requests.<sup>2</sup> Telemedicine is the way many, if not most, patients currently are being seen by clinicians. Many patients will continue to use this method even after the pandemic has waned. Telehealth has some specific effects on patients with bipolar disorder.

Video sessions and calls generally are very much welcomed by patients who are isolated to various degrees because of COVID-19. Their usual social outlets are diminished, and their access to in-person visits with clinicians is much reduced or eliminated. Hence, contact with an upbeat,

thorough, authoritative, and supportive consulting clinician can have a tremendous effect in reassuring patients that help is available. In fact, symptoms may diminish immediately during the call.<sup>3</sup>

Effort must be made, however, to deal effectively with wireless connectivity issues that may render speech garbled with dropped words or pronunciations that are difficult to understand.<sup>2</sup> It is important to slow down the conversation, adjust volume or microphone or video placement, be mindful of the time lag that can occur between speech and the transmission of the speech, and avoid interrupting the patient by responding too quickly. Video and phone transmission might make it difficult to determine if the patient is becoming tearful or agitated, and it is important to ask if this is occurring.

Another issue associated with the pandemic is the loss of usual routines of behavior associated with

previous mood states before isolation can result in new outlets (eg, buying online instead of in stores during manias). The clinician should be prepared to ask questions to uncover new syndromic behaviors.

Bipolar psychopharmacology issues that are relatively unique to the COVID-19 era were summarized in a recent review by experts from Spain.<sup>4</sup> Medication adherence is often reduced during isolation, so it is important (after establishing a therapeutic alliance using some of the previously noted suggestions) to inquire about adherence. Similarly, after examining the possible causes of nonadherence (eg, real or feared adverse effects, the feeling of being controlled by the medication, missing periods of euphoria), clinicians should educate their patients about the importance of adherence. Help may be needed from significant others in the household to monitor adherence, with the patient's permission.

The pandemic may be making it especially difficult to care for patients with bipolar disorder. What can—and should—you be doing to help them?

Substance use disorders may increase in severity in the isolation setting, and these should be ruled out or managed, if necessary. Patients may be fearful of initiating new medications without an in-person encounter, especially if bloodwork is required or patients have concerns about entering a medical facility for

testing.<sup>1</sup> The importance of lithium levels and kidney function tests will need to be reiterated and the benefits weighed against the risks associated with going to get the tests, which can be minimized with appropriate social distancing and masks.

There are some issues to consider with medications used in the treatment of patients who have COVID-19, if the patient requires hospital treatment.<sup>4</sup> Dexamethasone can induce mood switches to mania or depression. Dexamethasone's metabolism is induced by carbamazepine and, to a lesser extent, by oxcarbazepine. Initiation of these anticonvulsant mood stabilizers should therefore be avoided if possible. They also induce the metabolism of remdesivir, and carbamazepine may add to the risk of liver dysfunction caused by this antiviral agent. If the patient is already on one of these mood stabilizers, appropriate dosage adjustments of the COVID-19 drugs and

lab monitoring will be needed. Chloroquine and hydroxychloroquine should be avoided in patients with COVID-19 and bipolar disorder because they increase risk of mania, psychosis, and suicidal ideation.<sup>4</sup>

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## The One

*And Jesus was a sailor when he walked upon the water.*

—Leonard Cohen

Richard M. Berlin, MD

A hundred skaters in Christmas red circle the lake, bonfire smoke in the air, novices laughing before blade tips catch and knees kiss ice, my eyes searching for the one skater in every crowd who glides graceful as a god, like my father years ago in his black leather racing skates, long blades grabbing ice when he tucked low and tight, left arm behind his back, right arm beating time as he carved heavenly arcs, disciples sailing fast in his draft as they followed.

And since it is Christmas, my eyes search the crowd for Jesus, the one who walked to freeze, another Jew who davened in a prayer shawl like my father's and chanted the Sh'mah. I can see them skating together, my father's red scarf, Jesus' tunic a shiver of light as they mirror each other's form, an ache in their ankles, their joy of speed and wind and rhythm before they fell, two young men in search of miracles.



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# The Troublesome Tale of Cognitive Deficits in Patients at CHR for Psychosis

» Brian Miller, MD, PhD, MPH

## CASE VIGNETTE

“George” is a 15-year-old male in the 10th grade who is being evaluated by his school psychologist for declining academic performance. Last year, he earned grades of all As and Bs, but this year he has mostly Bs and Cs, with one D in an advanced math class. George has a 4-year history of generalized anxiety disorder, for which he takes a low-dose selective serotonin reuptake inhibitor. He has no active medical problems. He does not currently use tobacco, alcohol, or illicit drugs but admits to trying marijuana once at a party in the past year. There is no history of physical, sexual, or verbal abuse. He has a maternal aunt with chronic schizophrenia. His mother had gestational diabetes mellitus during her pregnancy with him, which was otherwise without complications. She states that he had frequent infections as a child and seemed to “get sick easily.” He has been slightly more irritable recently. George reports having a few close friends.

On interview, his affect is slightly restricted, but it brightens when he talks about his hobby (origami). He reported hearing whispering voices on a few occasions at night, which he attributed to noises outside his bedroom window. He reports this academic year it is harder for him to concentrate at school. Cognitive testing was notable for impairment in processing speed (about half standard deviation) and borderline impairment in visual learning compared with age- and sex-matched peers. His mother is concerned about his risk of schizophrenia.

Cognitive deficits are a well-replicated finding across the course of illness, including the psychosis prodrome, in schizophrenia.<sup>1,2</sup> There is evidence for cognitive decline in patients at clinical high risk (CHR) for psychosis compared with controls, with larger effect sizes in patients who transition to a psychotic disorder.<sup>3</sup> There is also meta-analytic evidence for broad cognitive impairments in memory, attention, verbal and visuospatial abilities, social cognition, and executive function in CHR patients.<sup>3</sup> Furthermore, cognitive deficits in CHR are independent predictors of conversion to psychosis and other outcomes, including role and social functioning.<sup>4,5</sup> Although it is not yet possible to definitively predict patients at CHR who will subsequently develop a psychotic disorder, this area of research offers visions of secondary and even primary prevention of psychosis. Is it possible to use cognitive testing, which is brief, easily performed, reliable, and noninva-

sive, to identify individuals at risk for psychosis? Similarly, among those at CHR, can cognitive testing predict who will convert to psychosis? What role does cognitive testing play in the clinical care of patients like George?

Cui and colleagues<sup>6</sup> aimed to relate baseline cognitive performance to a broad range of clinical outcomes at 1-year follow-up in patients at CHR of psychosis and controls from the ShangHai-At-Risk-for-Psychosis (SHARP) study, which launched in China in 2010. They hypothesized that patients with CHR who converted to psychosis (CHR-C) would have greater cognitive impairments than those who did not convert (CHR-NC), and both CHR groups would have greater cognitive impairments than healthy controls. They also analyzed outcomes in patients at CHR based on clinical status (trichotomized as remission, symptomatic, or poor outcome).

A total of 217 participants at CHR and 133 healthy controls from the

SHARP study completed the MATRICS Consensus Cognitive Battery (MCCB) at baseline and provided complete clinical data. These patients represented more than 90% of the patients who provided 1-year assessment data. The mean age of participants was aged 18.6 years; 47% were male; and all were lifetime psychotropic naïve at study entry. Subsequently, 80% of patients at CHR received antipsychotic medications. Inclusion criteria for all participants were aged 13 to 45 years, at least 6 years of education, and an available legal guardian for patients 18 years or younger. Participants with an IQ less than 70, severe somatic disease, and lifetime substance dependence were excluded. Psychotic disorder or prodromal symptoms in healthy controls were ruled out by structured clinical interview.

Raw scores on the MCCB were converted to Z-scores based on healthy control scores. The CHR group was divided into CHR-NC (n = 155) and CHR-C (n = 41) based on the 1-year follow-up assessment. In other analyses, the CHR group was trichotomized to 3 clinical outcomes at 1-year: CHR-remission (n = 102), CHR-symptomatic (n = 37), and CHR-poor outcome (n = 57). The CHR-remission group included patients with spontaneous remission or improvement with antipsychotic medication to mildly impaired ranges or better (Structured Interview for Prodromal Syndromes [SIPS] positive symptom scores  $\leq 2$ ) and global function at least 60 at follow-up. The CHR-symptomatic group included medicated participants with SIPS positive symptom scores of 3 to 5 and global function of at least 60 at follow-up. The CHR-poor outcome group included those who converted to psychosis (n = 41) and medicated patients with unremitting positive symptoms (SIPS positive symptom scores of 3 to 5) and poor global function (less than 60) at follow-up (n = 16). Data were analyzed using

multivariate analysis of variance with Bonferroni-adjusted post hoc pairwise comparisons between groups for MCCB scores. Effect sizes were calculated using Cohen's *d*.

There were no significant differences regarding age, sex, or education between CHR and healthy control groups. Cognitive scores were significantly lower than those for healthy controls on all MCCB subsets for all patients at CHR (effect sizes  $d = 0.37-0.95$ ), as well as the CHR-C (effect sizes  $d = 0.43-1.30$ ) and CHR-NC subgroups (effect sizes  $d = 0.39-0.91$ ) (Table). Participants in the CHR-C group performed significantly worse than those in the CHR-NC group on the Trail Making Test A (small-to-medium effect size,  $d=0.38$ ) and the Brief Visuospatial Memory Test-Revised (medium-to-large effect size,  $d = 0.69$ ).

**“Is it possible to use cognitive testing, which is brief, easily performed, reliable, and noninvasive, to identify individuals at risk for psychosis?”**

Compared with controls, CHR-remission and CHR-poor outcome scores were lower for all MCCB subsets (medium- to large-effect sizes for poor outcome,  $d = 0.35-1.91$ ), and CHR-symptomatic scores were lower for 6 of 8 MCCB subsets (effect sizes  $d = 0.50-0.93$ ). Furthermore, Brief Visuospatial Memory Test-Revised scores were significantly lower

**Table.** Effect Sizes for Cognitive Data for CHR Patients and Healthy Controls in the SHARP Study

Cognitive Domain	Test	CHR-C vs HC ( <i>d</i> )	CHR-NC vs HC ( <i>d</i> )	CHR-C vs CHR-NC ( <i>d</i> )
Processing speed	TMT-A	0.59*	0.38*	0.38*
	BACS SC	1.11*	0.91*	0.22
	Fluency	0.47*	0.58*	0.08
Verbal learning	HVLT-R	0.70*	0.72*	0.03
Visual learning	BVMT-R	1.30*	0.63*	0.69*
Working memory	WMS-III SS	0.55*	0.66*	0.14
Reasoning	NAB Mazes	0.78*	0.64*	0.16
Attention/vigilance	CPT-IP	0.43*	0.39*	0.07
	Processing speed composite	0.99*	0.86*	0.23

TMT-A, Trail Making Test, Part A; BACS SC, Brief Assessment of Cognition in schizophrenia: Symbol Coding; Fluency, Category Fluency-Animal Naming; HVLT-R, Hopkins Verbal Learning Test-Revised; BVMT-R, Brief Visuospatial Memory Test-Revised; WMS-III SS, Wechsler Memory Scale-Third Edition: Spatial Span; NAB Mazes, Neuropsychological Assessment Battery: Mazes; CPT-IP, Continuous Performance Test-Identical Pairs; CHR-C, CHR converters to psychosis; CHR-NC, CHR non-converters

\*  $p < 0.05$

in the CHR-poor outcome versus CHR-remission group (medium effect size,  $d = 0.53$ ).

The authors noted that an educated, mostly urban Chinese sample of patients at CHR had cognitive impairments of a similar magnitude to a western prodromal consortium (the North American Prodrome Longitudinal Study [NAPLS]), with evidence for greater impairments in those who converted to psychosis at 1-year follow-up (versus non-converters). Findings advance our understanding of cognitive heterogeneity in patients at CHR of psychosis. The relatively small sample size of some CHR subgroups and 1-year (versus a longer follow-up) duration were noted as potential study limitations.

### Matters to consider

An important question follows: what is the evidence for the feasibility and efficacy of strategies or treatment for cognitive impairments in patients at CHR of psychosis? Do they forestall or decrease conversion to psychosis, or are they associated with improvements in other outcomes? To date, there are small studies that have in-

vestigated cognitive interventions in this population. Several studies have investigated computer-based cognitive training in participants with CHR.<sup>7-10</sup> Rauchensteiner and colleagues<sup>7</sup> found that cognitive training was associated with significant improvements in verbal learning and memory. Another study by Hooker et al<sup>8</sup> found significant improvement in processing speed and trend-level improvements in visual learning, visual memory, and global cognition. By contrast, a small double-blind randomized trial by Piskulic and colleagues<sup>9</sup> did not find significant effects on cognition between cognitive training and an active control (computer games). A larger double-blind randomized controlled trial of the same interventions used in the negative trial by Piskulic et al<sup>9</sup> found significant improvements in verbal memory in the cognitive training (versus computer games) group. Recently, a randomized trial of an integrated social- and neuro-cognitive remediation intervention that included a combination of individual, group, in-person, and computer-based training—versus enriched ac-

ceptance and commitment therapy—found improvements in social cognition and a trend for improved reaction time.<sup>11,12</sup> Overall, these studies demonstrate the feasibility of and point to potential efficacy of cognitive interventions in CHR. Future studies are needed to investigate the optimal type and “dose” of cognitive training in patients at CHR, as well as the impact on symptoms, functioning, and conversion to psychosis.

This study demonstrates the feasibility of harmonizing measures across different geographical locations for the reliable and valid assessment of cognition in patients at CHR of psychosis. Furthermore, findings replicate, and therefore reinforce, earlier studies, as the pattern and magnitude of cognitive impairments in patients at CHR were similar between the SHARP study and the NAPLS consortium.

Based on these data, cognitive impairments represent an important, viable target for intervention in this population.

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## PAIN MANAGEMENT

Pain and Smoking:  
Is There an Association?

» Steven A. King, MD, MS

The association between smoking cigarettes and the risk of developing serious and potentially fatal health problems (most notably cardiovascular diseases, pulmonary diseases, and cancer), has long been accepted fact. However, an additional health problem that may also be associated with smoking has often been overlooked: pain.

Two recent papers indicate a strong association between smoking and pain.

The first is a literature review of the current research on the subject.<sup>1</sup> Among the review's important findings is that those who suffer from chronic pain are substantially more likely to smoke than are those who do not suffer from chronic pain. Although smoking rates continue to decline in the latter group, this does not appear to be occurring in those with pain.

Cigarette smoking has been cited as a risk factor for a wide variety of painful conditions, including back pain, headache, and diabetic peripheral neuropathy. Smoking appears to be associated with both the development and severity of pain.

The second paper specifically studied the most likely locations of pain among individuals who smoke. The study examined data from a 2003 to 2004 National Health and Nutrition Examination Survey, which contained data from comprehensive bodily pain questionnaires in addition to questions on other health issues, including tobacco use.<sup>2</sup> The study compared 1054 participants who smoked tobacco with 1316 participants who did not.

Those who smoked were found to be more likely to suffer chronic pain. Although the likelihood of pain was increased throughout the body, the study found that spine pain, and especially low back pain, had the strongest association with smoking. The second strongest association was between headaches and smoking. Smoking was also associated with both trunk pain, which included the chest and abdomen, and limb pain. (All statistical associations were drawn from Smuck et al.<sup>2</sup>)

This is an interesting and perhaps an unexpected finding. Because of the association between smoking and cardiovascular and cerebrovascular problems, it is easy to see why headaches would be fairly common among individuals who smoke. However, it might be reasonably expected that pain in the trunk and limbs would be more common than pain in the spine. The authors suggest that vascular factors may play a greater role in back pain than is often thought.

Whether e-cigarettes, which are becoming more

popular, are any less associated with pain than traditional cigarettes remains an unanswered question.

From personal experience treating patients with chronic pain who also smoke, I know that helping them with smoking cessation attempts can be challenging. Although most patients are often well aware of the risks associated with smoking, their pain and its impact on their lives may make it more difficult for them to quit. Their pain may make them feel restricted, and their ability to participate in previously enjoyable activities is limited. Smoking is among the few such activities in which they can still indulge. They may also feel that smoking helps them cope with the pain.

Some evidence indicates that nicotine may have some analgesic effects, but abstaining from smoking may cause individuals to suffer hyperalgesia, a lowering of the pain threshold.<sup>3,4</sup> Thus, those who smoke may receive temporary relief from tobacco use, and their pain may get worse when they try to stop.

Additionally, depression and anxiety are frequent comorbidities among those with chronic pain, and their presence can also contribute to the challenge of getting patients to stop smoking.<sup>5</sup>

Ultimately, all evidence points to the importance of convincing patients with chronic pain who also smoke that tobacco is not helpful. Indeed, tobacco may be significantly exacerbating their pain and adding to their misery.

The multitude of challenges can understandably make it difficult to persuade patients with chronic pain to stop using tobacco. Unfortunately, only a limited number of studies have sought to investigate the best treatments for attaining this goal.<sup>6</sup>

Although no single optimal treatment has yet been identified, it appears that while nicotine replacement therapy can be useful, the interventions that are most successful are those that address both the pain and the smoking using psychotherapeutic interventions.<sup>7</sup> In this way, treating tobacco use disorder and comorbid chronic pain is similar to the treatment of pain and iatrogenic opioid use disorder, where both problems must be managed

together to be successful in treating either.

Of course, this raises the important issue of who treats pain and how it is treated. (*For more information on psychiatry and pain, see Psychiatric Times™ November 2020 Special Report.*)

For the most part, the management of chronic pain has been under the aegis of anesthesiology, followed by physiatry and neurology, with psychiatry far down the list. However, the order of these specialties would be reversed if we asked which is best able to aid in smoking cessation. One doubts that there are many anesthesiologists, psychiatrists, or neurologists who have expertise in treating patients with nicotine addiction.

As a result, it is difficult for patients with chronic pain who smoke to find health care professionals qualified to treat both issues. If it appears to patients that smoking and pain are 2 separate problems that require different medical specialties to treat them, it may make it more difficult to convince them that the issues are actually entangled. Nonetheless, the evidence suggests that managing 1 issue may aid in managing the other.

Dr King is in private practice in Philadelphia.

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Brief Summary of Prescribing Information for Drizalma Sprinkle™ (duloxetine delayed-release capsules). This Brief Summary does not include all the information needed to use Drizalma Sprinkle™ safely and effectively. See full Prescribing Information for Drizalma Sprinkle™.

**WARNING: SUICIDAL THOUGHTS AND BEHAVIORS**

**See full prescribing information for complete boxed warning.**

**Increased risk of suicidal thinking and behavior in pediatric and young adult patients taking antidepressants.**

**Closely monitor all antidepressant-treated patients for clinical worsening and for emergence of suicidal thoughts and behaviors.**

## INDICATIONS AND USAGE

Drizalma Sprinkle™ (duloxetine delayed-release capsules) is a serotonin and norepinephrine reuptake inhibitor (SNRI) indicated for:

- Major Depressive Disorder (MDD) in adults
- Generalized Anxiety Disorder (GAD) in adults and pediatric patients aged 7 to 17 years old
- Diabetic Peripheral Neuropathic Pain (DPNP) in adults
- Chronic Musculoskeletal Pain in adults

## CONTRAINDICATIONS

**Serotonin Syndrome and MAOIs:** Do not use MAOIs intended to treat psychiatric disorders with Drizalma Sprinkle™ or within 5 days of stopping treatment with Drizalma Sprinkle™. Do not use Drizalma Sprinkle™ within 14 days of stopping an MAOI intended to treat psychiatric disorders. In addition, do not start Drizalma Sprinkle™ in a patient who is being treated with linezolid or intravenous methylene blue.

## DOSAGE AND ADMINISTRATION

- Drizalma Sprinkle™ can be taken with or without food. Drizalma Sprinkle™ may be swallowed whole (do not crush or chew capsule); opened and sprinkled over applesauce; or administered via nasogastric tube
- Missed doses should be taken as soon as it is remembered. Patients should not take two doses of Drizalma Sprinkle™ at the same time
- There is no evidence that doses greater than 60 mg/day confers additional benefit, while some adverse reactions were observed to be dose-dependent

## WARNINGS AND PRECAUTIONS

- **Hepatotoxicity:** Hepatic failure, sometimes fatal, has been reported in patients treated with duloxetine delayed-release capsules. Duloxetine delayed-release capsules should be discontinued in patients who develop jaundice or other evidence of clinically significant liver dysfunction and should not be resumed unless another cause can be established. Drizalma Sprinkle™ should not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease
- **Orthostatic Hypotension, Falls, and Syncope:** Cases have been reported with duloxetine delayed-release capsules therapy
- **Serotonin Syndrome:** Increased risk when coadministered with other serotonergic agents (eg, SSRI, SNRI, triptans), but also when taken alone. If it occurs, discontinue Drizalma Sprinkle™ and initiate supportive treatment
- **Increased Risk of Bleeding:** Duloxetine may increase the risk of bleeding events. A post-marketing study showed a higher incidence of postpartum hemorrhage in mothers taking duloxetine. Concomitant use of NSAIDs, aspirin, other antiplatelet drugs, warfarin, and anticoagulants may increase this risk

- **Severe Skin Reactions:** Severe skin reactions, including erythema multiforme and Stevens-Johnson Syndrome, can occur with duloxetine. Drizalma Sprinkle™ should be discontinued at the first appearance of blisters, peeling rash, mucosal erosions, or any other sign of hypersensitivity if no other etiology can be identified
- **Discontinuation Syndrome:** Taper dose when possible and monitor for discontinuation symptoms
- **Activation of Mania or Hypomania:** Use cautiously in patients with bipolar disorder. Caution patients about the risk of activation of mania/hypomania
- **Angle-Closure Glaucoma:** Avoid use of antidepressants, including Drizalma Sprinkle™, in patients with untreated anatomically narrow angles
- **Seizures:** Prescribe with care in patients with a history of seizure disorder
- **Blood Pressure:** Monitor blood pressure prior to initiating treatment and periodically throughout treatment
- **Hyponatremia:** Can occur in association with SIADH. Cases of hyponatremia have been reported
- **Glucose Control in Diabetes:** In diabetic peripheral neuropathic pain patients, small increases in fasting blood glucose and HbA<sub>1c</sub> have been observed

## ADVERSE REACTIONS

Most common adverse reactions (≥5% and at least twice the incidence of placebo patients) nausea, dry mouth, somnolence, constipation, decreased appetite, and hyperhidrosis.

## DRUG INTERACTIONS

- Potent CYP1A2 Inhibitors: Avoid concomitant use
- CYP2D6 Substrates: Consider dose reduction with concomitant use

## USE IN SPECIFIC POPULATIONS

- **Hepatic Impairment:** Avoid use in patients with mild, moderate, or severe hepatic impairment
- **Renal Impairment:** Avoid use in patients with severe renal impairment
- **Pregnancy:** Third trimester use may increase risk of symptoms of poor adaptation (respiratory distress, temperature instability, feeding difficulty, hypotonia, tremor, irritability) in the neonate. Advise patients that Drizalma Sprinkle™ use during the month before delivery may lead to an increased risk for postpartum hemorrhage and may increase the risk of neonatal complications requiring prolonged hospitalization, respiratory support and tube feeding.
- **Lactation:** Advise breastfeeding women using duloxetine to monitor infants for sedation, poor feeding and poor weight gain and to seek medical care if they notice these signs.

To report SUSPECTED ADVERSE REACTIONS, contact Sun Pharmaceutical Industries, Inc. at 1-800-818-4555 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

Please read full Prescribing Information and Medication Guide for Drizalma Sprinkle™ and discuss any questions with your doctor.

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PM-US-DRI-0099



# Underused Medication May Be Best Bet for Comorbid AUD and Depression

» Chris Aiken, MD

In a network meta-analysis of alcohol use disorders (AUD) with depression, one medication stood out as the most effective but is not widely used. The meta-analysis, which included 66 randomized controlled trials that tested 18 categories of medications in 5890 patients who had an AUD and either major depression or depressive symptoms, found that disulfiram was the most effective at reducing alcohol use across all comparisons.<sup>1</sup>

Only 3 medications reached statistical significance for remission: disulfiram, anticonvulsants (carbamazepine, topiramate, tiagabine), and a naltrexone with a selective serotonin reuptake inhibitor (**Figure 1**). The odds ratio for remission was much higher with disulfiram, although the spread of the data was also wider as indicated by the standard deviations in the graph. This difference held up to sensitivity analysis, in which studies that might have skewed the results were removed.

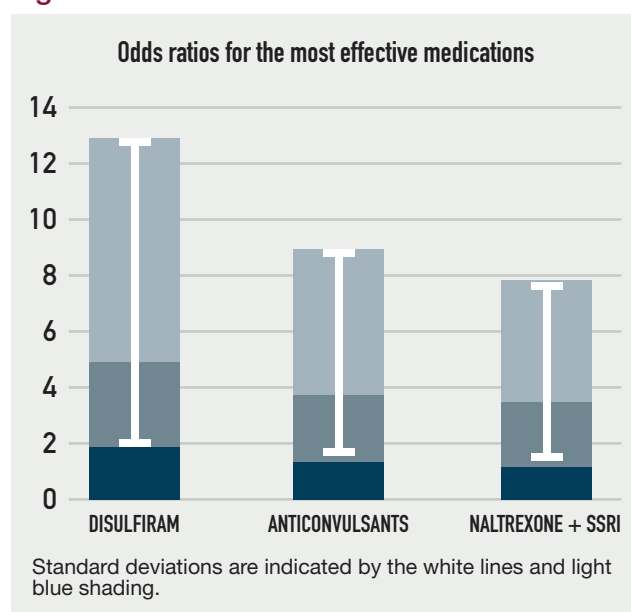
For abstinence, only disulfiram and baclofen reached statistical significance. (Baclofen is a muscle relaxant with mixed results in AUD when studied independent of depression. It has no measurable reinforcing properties; there have been rare reports of baclofen abuse.) The odds ratio for days abstinent was higher for disulfiram compared with baclofen; this finding held up to sensitivity analysis (**Figure 2**).

For change in depressive symptoms, there were no clear winners. The noradrenergic medications appeared effective as a group, but this group included only venlafaxine and the non-US medication viloxazine. Nearly all efficacy was attributable to viloxazine, a norepinephrine reuptake inhibitor. Mirtazapine showed promise, but only in a secondary analysis of studies looking at full episodes of depression, rather than subsyndromal cases.

Although these studies cannot explain why disulfiram works well in depression, I will venture a guess from clinical experience. Patients with depression are often unable to take action on the things that are good for them, ie, bathing, eating healthy, and achieving sobriety. Although they want to stop drinking, they struggle with ruminative thoughts and never arrive at an executable plan. Disulfiram halts indecision, relieving them of the struggle. Patients are unlikely to drink on disulfiram because their actions are driven more by anxious avoidance than by impulse.

Disulfiram's efficacy may not be unique to depression. The drug worked well in general AUD in prior analyses. In the 1930s, workers who were exposed to it at a rubber factory became sick after drinking alcohol. This led to the first clinical use in the 1940s and

**Figure 1. Alcohol Remission Rates**



its FDA approval for alcohol cessation in 1951. However, only 200,000 individuals—about 1% of patients with AUD—take disulfiram in the US.

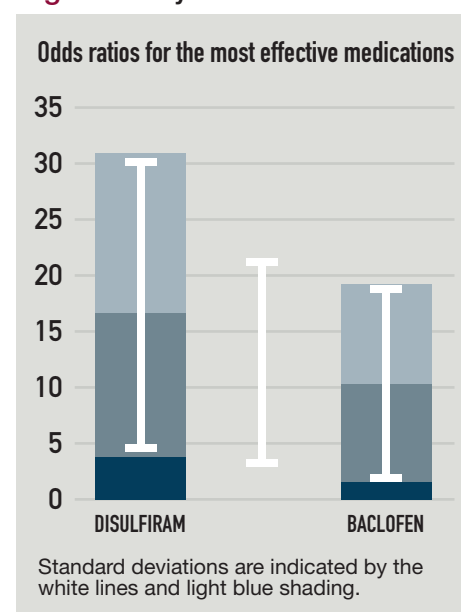
The reason for disulfiram's decline may be due to its unique mechanism. Disulfiram induces an immediate hangover reaction when combined with alcohol. It blocks the enzyme that metabolizes acetaldehyde, the toxin responsible for alcohol's hangover effect. With heavy drinking or high doses of disulfiram, this effect can be fatal. When disulfiram was first released, that effect was thought to be necessary, so patients were advised to drink. That practice ended when a few patients died, but it also left a stain on disulfiram's reputation.

Oncologists do not withhold lifesaving medications because they are potentially toxic. Yet disulfiram appears underutilized, despite the fact that alcohol-related fatalities have soared to the No. 1 cause of death in middle-aged adults. Although fatalities are extremely rare with disulfiram, physicians may feel a greater weight of responsibility for those deaths than they do when patients die from alcohol. An oncologist, however, would not feel this way when a patient dies from cancer.

As a review of disulfiram's safety noted, "Deaths from the disulfiram-alcohol (ethanol) interaction have not been reported in recent years, possibly because the dosages used are lower than those used 40 years ago and patients with cardiac disease are now excluded from treatment."<sup>2</sup>

Today, most physicians prefer the lower dose of 250 mg/day. This produces a less toxic interaction with alcohol and works just as well as 500 mg/day. Actually, placebo worked just as well as disulfiram in

**Figure 2. Days Abstinent From Alcohol**



the blinded studies because simply warning a patient that the interaction is toxic will help them achieve sobriety even when the pill is a placebo.

Patients must be alcohol free for 12 hours before starting disulfiram; the disulfiram-alcohol interaction persists for up to 2 weeks after stopping disulfiram. Disulfiram is contraindicated in severe coronary artery disease or heart failure, as there have been cases of sudden death after drug initiation. Relative contraindications include liver disease (disulfiram can elevate liver function tests, as can naltrexone), psychotic disorder (there are rare cases of psychosis or confusional states), and active alcohol use (in the past 12 hours). When used in absence of alcohol, common adverse effects include fatigue and headache. Check for drug interactions in the cytochrome P450 enzyme system before starting it.

The bottom line seems pretty straightforward: Don't overlook disulfiram, but know how to use it safely in AUD.

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## CLINICAL

# Care of Youth Hospitalized With Somatic Symptom and Related Disorders

» Tareq Yaqub, MD, Bernard Biermann, MD, PhD, Laura Andersen, MD, MPH, and Nasuh Malas, MD, MPH

Somatic symptom and related disorders (SSRDs) are a set of psychiatric conditions characterized by physical symptoms that are inconsistent with physical disease and influenced by psychological factors. They are common in pediatric medicine, with prevalence rates ranging from 13% to 50% depending on the setting. Across all ages, SSRDs account for nearly 20% of health care spending annually.<sup>1</sup> Additionally, a small subset of patients have multiple somatic complaints and tend to access crisis and emergency services and hospital services at higher rates. They also have high recidivism rates.<sup>2</sup>

Despite the recognition of the impact of SSRDs on pediatric health care, clinicians and patients/families continue to be frustrated with the evaluation and management of these conditions.<sup>1</sup> Without early incorporation of a broader biopsychosocial conceptualization, there can be an undue focus on disability, impairment, and somatic complaints. This leads to low-yield diagnostic testing and increased polypharmacy interventions

that do not address the rehabilitative needs of the patient and family.<sup>2,3</sup> In the absence of an explanatory model for symptoms, patients and families may feel they are being dismissed, creating a dynamic of mistrust between patients/families and the medical system. Ultimately, without a clear road map for evaluation and management, care can be inconsistent and misuse of health care resources may occur, which, in turn, can lead to poor outcomes.

As SSRDs most often present in nonpsychiatric settings, a patient's first contact with a mental health care provider may be through psychiatric consultation in the emergency department or in a hospital setting. Therefore, psychiatric consultation

should be considered as early as possible to foster the perception that consultation-liaison (CL) psychiatrists are an integral part of the multispecialty team.

SSRDs account for approximately 15% to 20% of psychiatric consults in the pediatric hospital setting and have been reported as the second most common reason for consultation after suicide assessments.<sup>4,5</sup> As such, there is a growing effort to standardize the evaluation and management of pediatric SSRDs. Most recently, the American Academy of Child and Adolescent Psychiatry (AACAP) published a Clinical Consensus Pathway for SSRD Evaluation and Management.<sup>3</sup>

## SIGNIFICANCE FOR PRACTICING PSYCHIATRISTS

- SSRDs are common disorders seen in pediatric medical settings, accounting for approximately 15% of all psychiatric consults in the pediatric hospital setting.
- Early involvement of psychiatry in the evaluation of youth with SSRDs may reduce length of stay and hospital-related cost.
- Treatment of SSRDs optimally involves a multidisciplinary approach and clear, consistent messages regarding conceptualization of illness and treatment goals.
- Discharge planning is an important element of SSRDs treatment and should include determining the best setting for longitudinal management and coordinating follow-up care with psychology, psychiatry, primary care, subspecialty pediatricians and, as needed, physical therapy, occupational therapy, and speech and language pathology.

## Epidemiology

Most SSRDs are seen in nonpsychiatric settings, with approximately 6% of hospitalized children relaying symptoms consistent with an SSRD.<sup>2</sup> The most common complaints include neurologic symptoms, pain, gastrointestinal distress, and fatigue.<sup>6</sup> SSRDs can present at any age, but they are more common and less problematic in prepubertal youth, with increasing impairment and pathology in adolescents.<sup>7,8</sup> Prevalence rates are equal across sexes prior to puberty; after puberty, higher prevalence is seen in female sex.<sup>9,10</sup> Although psychological trauma, particularly sexual trauma, is a well-associated risk factor for SSRDs in adults, it is not necessarily associated with SSRDs in youth.<sup>9</sup> However, if present, trauma in youth with SSRDs often results in a more complicated treatment course, more severe symptoms, and increased risk for need of higher levels of psychiatric care.<sup>11</sup>

## Evaluation, Collaboration

The evaluation and management of youth experiencing an SSRD are predicated on early recognition of risk factors (Table 1). The foundation of an SSRD evaluation is built on concurrent mental health and physical health evaluation, unified evidence-based language that is con-

## CASE VIGNETTE

"Julie," a previously physically healthy 12-year-old female, presented with 6 months of abdominal pain, weight loss, and emesis that began shortly after her parents divorced. As a result, she missed several weeks of schooling.

Work-up included a complete blood count, comprehensive metabolic profile, thyroid studies, C-reactive protein test, erythrocyte sedimentation rate, abdominal x-ray, abdominal ultrasound, upper and lower endoscopy, and stool culture, all of which were unremarkable. Eliminating gluten from her diet was not helpful. The patient had no previous physical health concerns, including no previous gastrointestinal pathology. There was no history of substance use, sexual activity, psychological trauma, or abuse.

Julie was admitted for her fourth medical admission within 4 months. Child and adolescent psychiatry was consulted for evaluation of anxiety. Julie and her parents were skeptical about any psychological factors influencing her presentation and

were hesitant to agree to psychiatric consultation. The parents were advocating for the use of opioids for her pain and an expanded work-up.

The patient received concurrent evaluation by the pediatric hospitalist service, gastroenterology, psychology, and psychiatry. No further diagnostic testing was pursued. The team found Julie had comorbid learning difficulties, nonspecific anxiety, maladaptive coping, and increased familial expressed emotion contributing to her presentation in the context of the recent divorce. A multidisciplinary meeting was held with Julie and her parents to discuss the diagnosis of somatic symptom disorder (DSM-5 300.82). The family was presented with a conceptual framework for symptom development by the multidisciplinary care team, in addition to biopsychosocial contributors to her presentation and a future management plan.

Julie was referred for outpatient cognitive behavioral therapy and prescribed mirtazapine 7.5 mg at bedtime for anxiety and sleep difficulties. Her symptoms improved by discharge, and she was minimally symptomatic upon follow-up with her primary care provider.

sistent across disciplines, and direct communication with the family regarding the multifactorial nature of SSRD presentation. Care of youth with SSRDs requires close interprofessional team support. This includes collaboration among the primary care physician (PCP), emergency physician, hospitalist physician, nursing, social work, child life, rehabilitative staff, subspecialty pediatricians, and CL psychiatrist/psychologist. Roles should be delineated early in the management course.

CL psychology/psychiatry should be consulted at the earliest suspicion of an SSRD to normalize psychiatric involvement in comprehensive care. Beyond assessment, CL psychology/psychiatry can aid with framing conversations with the patient and family, providing evidence-based interventions, and addressing psychiatric comorbidities. Although SSRDs do not necessarily accompany other discrete psychiatric conditions, anxiety disorders and mood disorders may be present in up to 50% of youth with SSRDs. These comorbidities should be incorporated in the case formulation for proper management of these conditions.<sup>6,9</sup> Ultimately, this process is dynamic and highly interactive and should adapt to the needs of the patient and family.

Discussion of symptom development and diagnostic conceptualization should be paired with management strategies, highlighting the multifactorial contributors to symptom development. Pairing the multiple biopsychosocial factors allows for a coherent, systematic approach to rehabilitative care, psychotherapeutic management, and judicious use of targeted psychopharmacology. Joint communication by all involved physicians and other clinicians using consistent DSM-5 language and clear discussions of a conceptual framework for symptom development, highlighting mind-body interactions, are crucial.

Once the evaluation is complete and the diagnosis of SSRD is confirmed, it is helpful to have an interprofessional care meeting with the patient family to share the diagnosis. Explaining a conceptualization of how symptoms formed, progressed, and continue to present—along with the related biopsychosocial factors influencing presentation—is the most critical part of this conversation. This is accomplished via joint physical health and mental health providers using consistent DSM language with the relationship of physical, environmental, psychological, social, and cognitive factors to symp-

tom development. For the patient and family to invest in the diagnoses and partner in the ongoing management of SSRD, they must understand this conceptualization.

Importantly, clinicians should gauge the patient's and family's readiness to accept the information. As such, communication must be geared to the individual's understanding, values, and readiness. It is often valuable to pair discussions with the use of motivational interviewing to enhance engagement and understand the patient's or family member's experience. Discussions may start with a more biological conceptualization, emphasizing concepts such as somatosensory amplification and visceral hypersensitivity; analogies may be used to highlight mind-body interactions. Some families may be able to appreciate and incorporate psychological constructs earlier in the discussion of this conceptual framework. It is important to validate emotions while shifting discussions to functionality. Patients may want to focus on their impairment; it is, therefore, important to pivot conversation to highlight strengths, abilities, and incremental improvements.

### Treatment Management

Management of an SSRD in youth is an iterative process that begins with setting clear goals and expectations. Misalignment of expectations is often a point of conflict. Patients and families may expect complete resolution of symptoms following initial encounters. Here, psychoeducation is key to the initial framing of the concept of somatization, discussing mind-body interactions, and describing joint medical and psychiatric management. Cognitive behavioral therapy (CBT) has a strong evidence base in addressing psychological factors underpinning pediatric SSRD.<sup>12</sup> CBT aids in greater awareness of how cognition, emotions, and other psychological processes impact physical sensations, and it empowers the patient with strategies to dampen somatic complaints. It focuses on improving functioning in small, achievable steps while shifting the focus away from impairment.

CBT psychotherapy can occur in tandem with delivery of rehabilitative services. As many as 50% of youth with an SSRD will have a comorbid depressive or anxiety disorder, making treatment of psychiatric comorbidities an important component of SSRD management.<sup>5</sup> Close involvement with the PCP is necessary, including proactive, regularly scheduled brief visits. These visits

should be used to coordinate services, address questions, monitor progress, provide reassurance, and promote functioning. PCPs should conduct judicious evaluations of new concerns, collaborating with psychiatry, psychology, and subspecialty pediatrics as needed. In this way, the propensity to seek care in crisis and pursue care in a disjointed fashion can be extinguished over time.

Care should be provided in the setting that best matches the patient's needs and severity of illness. For youth with severe worsening of function without a clear diagnostic understanding, medical admission may be warranted for further evaluation and management. Youth with significant psychiatric comorbidity may benefit from inpatient or partial psychiatric hospitalization. Those patients with significant rehabilitative needs will benefit from intensive outpatient or inpatient rehabilitation. Most youth, however, can be successfully managed in the outpatient setting with regular PCP evaluations, ongoing psychotherapy, and psychiatric care, as well as additional rehabilitative and pediatric subspecialty follow-

up.<sup>1</sup> This approach, which aligns with national consensus, provides the best framework for youth to regain functioning, improve symptomatically, and succeed in the care of SSRD.<sup>2,13</sup>

### Role of the CL Psychiatrist

Care of youth with SSRDs highlights the important liaison role of CL psychiatry. CL psychiatrists aid in the dissemination of information and develop a shared understanding with the patient and family; they also support appropriate language use and incorporate psychological, social, psychiatric, familial, and cognitive factors in the overall assessment with the larger care team. This should include clearly defining care team roles, as well as setting expectations with patients and their families (Table 2).

The CL psychiatrist should describe mind-body interactions using analogies that simplify understanding for the patient and family. For example, a computer analogy helps explain SSRDs, in which physical disease is more akin to a hardware problem and psychosocial and environmental factors are more akin to a software issue. Similarly, it can be helpful to describe SSRDs as the

**Table 1. Risk Factors for the Development and Perpetuation of SSRDs in Youth**

<b>Biological and genetic</b>	<ul style="list-style-type: none"> <li>Abnormal somatosensory perception</li> <li>Overly reactive sensory perception neurocircuitry</li> <li>Smaller amygdala volumes</li> <li>Overactive hypothalamic-pituitary-adrenal axis</li> <li>Sensitive sympathetic nervous system</li> <li>Conditioned physiologic response to distress</li> </ul>
<b>Associated demographic features</b>	<ul style="list-style-type: none"> <li>Female sex (postpuberty)</li> <li>White</li> <li>Adolescent age</li> <li>History of physical disease</li> </ul>
<b>Psychological</b>	<ul style="list-style-type: none"> <li>Internalizing coping style</li> <li>Avoidant coping</li> <li>Perfectionism</li> <li>Overly pessimistic cognitions</li> <li>Shy temperament</li> <li>Strong emotional reactivity</li> </ul>
<b>Psychiatric</b>	<ul style="list-style-type: none"> <li>Depression</li> <li>Anxiety</li> <li>Posttraumatic stress disorder</li> </ul>
<b>Cognitive</b>	<ul style="list-style-type: none"> <li>Lower intellectual ability</li> <li>Learning disabilities</li> </ul>
<b>Social</b>	<ul style="list-style-type: none"> <li>History of victimization of bullying</li> <li>Difficulty with interpersonal relationships</li> </ul>
<b>Familial</b>	<ul style="list-style-type: none"> <li>Parental catastrophizing and excessive focus on physical symptoms</li> <li>High expressed emotion</li> <li>Parent-child conflict</li> <li>Poor parental modeling of coping</li> <li>Familial history of depressive disorders, anxiety disorders, substance use disorders, or unexplained medical concerns/SSRDs</li> </ul>

**Table 2. Expectation Setting and Goals of Care**

- Identify etiologic factors influencing clinical presentation and perpetuation of symptoms.
- Provide some level of symptom relief; complete relief may be unrealistic and should be discussed early to align expectations with the care team and patient/family.
- Articulate a conceptual framework for how symptoms developed, and highlight the multifactorial nature of symptom development.
- Establish a template for management with a multidisciplinary care team, including engagement with primary care, outpatient mental health providers, and school representatives.

body's alarm system being overactive or hypersensitive to somatosensory interactions, which can lead to identification of factors that can heighten or dampen normative reactions to bodily sensations. The goal is to aid patients and families in understanding the interplay of physiologic, psychological, social, and emotional factors that influence somatic symptoms.

Given the diverse and wide-ranging issues and the number of team members involved in effective SSRD care, the CL psychiatrist should also be at the forefront in aiding standardization of multidisciplinary, evidence-based interventions. This should be informed by existing consensus guidelines, such as those published by the AACAP in 2020, and local resources, systems of care, and practice experiences.

CL psychiatrists may be asked about the use of psychopharmacology in managing SSRDs. There is no evidence to demonstrate that psychopharmacology can directly ameliorate

the symptoms of SSRDs, and this should be expressed clearly to patients and families as well as to the larger care team.<sup>14</sup> At times, youth and families may become frustrated that psychopharmacology has not resulted in resolution of symptoms. Therefore, it is important to reiterate, early on, that management of SSRDs is predicated on a multidisciplinary approach that targets the factors fostering symptom-development and persistence. Here the focus is shifted to improvement in functioning and incremental rehabilitation of cognitive, emotional, and physical health factors.

Psychopharmacology can be helpful in addressing psychiatric comorbidities and may provide more immediate relief for other psychiatric factors resulting in acute distress. When provided, psychopharmacological options should have clear targets for management with clear expectations within the greater context of treatment. It is important to explore familial expectations and continue to

set realistic expectations, emphasizing the importance of ongoing engagement with other care teams, including psychology and rehabilitative services.

### Concluding Thoughts

CL psychiatry can also have an important role in informing longitudinal management of SSRDs, which may be accomplished through collaborative clinical models. Such models often have psychiatry and psychology providing integrated care in a primary care or subspecialty pediatric practice. Inpatient psychiatric care may be needed for young patients with severe psychiatric comorbidities, safety concerns related to suicidal ideation or behavior, or severe psychological trauma. Ultimately, disposition planning must account for the level of training, experience, resources, and standardization of practice that exists within different settings in a given health system.

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# Spike in Health Care Cyber Attacks

» Keith A. Reynolds

Nefarious characters ramped up their cyber attacks on health care institutions as 2020 came to an end. According to a report from Check Point Software Technologies LTD, there was a 45% increase in cyber attacks targeting global health care organizations from the beginning of November 2020 through the end of the year. This was more than double the increase in cyber attacks across other industries worldwide across the same period. Although the attacks involved a variety of methods, the report found the largest increase in ransomware attacks.

An October alert from the Cybersecurity & Infrastructure Security Agency (CISA), the Federal Bureau of Investigation (FBI), and the Department of Health & Human Services (HHS) said that the agencies had credible information about increased and imminent cybercrime threat to US hospitals

and health care providers. These agencies believed the goal was to spread the Ryuk ransomware for financial gain.

Hospital and health systems are an attractive target because patient safety and well-being hang in the balance. In September 2020, Universal Health Services, one of the United States' largest hospital and health care networks, was a victim of such an attack. Employees believed the attack had the hallmarks of Ryuk, according to *Wired* magazine. Linked to Russian cybercriminals, Ryuk first appeared in 2018. It has been used to attempt to extort large amounts of ransom from corporations with deep pockets.

The Check Point Report speculated that because these ransomware attacks result in cash windfalls for the hackers, it makes them hungrier for more. Plus, with the world's health care systems preoccupied with the coronavirus disease 2019 pandemic, the industry has become a prime target.

### Check Point provided tips to help prevent ransomware and phishing attacks:

- **Look for Trojan infections.** Most ransomware attacks start with an initial infection by a Trojan that can occur days or weeks before the ransomware attack.
- **Raise your guard on weekends and holidays.** Most ransomware attacks occur when information technology and security staff are out of the office.
- **Educate employees about malicious emails.** Ensuring employees know how to identify and avoid possible ransomware attacks is critical, as many attacks start with a targeted phishing email that does not contain the malware. □

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## Book Review

# What was life like in the 1950s Bronx for a budding preeminent psychiatrist?

*Dr Sharfstein was one of many preeminent psychiatrists who reached out to review this book. The number of friends that Dr Sederer has, the number of psychiatrists who have worked for him or with him and hold him in such high regard, is truly impressive.*

—Howard Forman, MD, Book Review Editor

Reviewed by Steven S. Sharfstein, MD

One of the few benefits of pandemic-driven social isolation and quarantine is time to read. Really read. Newspapers and magazines as well as fiction and nonfiction. It was my special enjoyment to pick up the memoir of Lloyd Sederer, MD, *Ink-Stained for Life*. Disclosure: I have known the author for many years and consider myself a friend and close colleague, but I did not know the Lloyd (and I will use his first name throughout this review as the memoir is about his youthful years) that is contained within these 200-plus pages. I feel that my conflict does not prevent me from reviewing this memoir, and it also gives me the pleasure of recognizing the adult Lloyd in the context of his growing years. He is one of the preeminent psychiatrists in America today as a clinician, teacher, author, and public health leader.

The book consists of 14 chapters that are stories or vignettes from Lloyd's New York City (the Bronx, in particular) experiences in the 1950s and 1960s. Each story is paired with a companion essay on the meaning of the experience or memory, and the context at that time and place and in light of today's social issues. His insights as a psychiatrist are shared throughout, and these are the key observations that lead me to hope that practicing psychiatrists will avail themselves of this easy-to-read volume.

Lloyd's childhood and adolescence were remarkably benign or normal. No major trauma or losses to overcome. It was full of love and family. He did not have to overcome poverty or discrimination. There was struggle, however: the struggle of a first-generation immigrant family and small business owner; the struggle of a rebellious, odd child who fashioned his identity against the backdrop of constraints of his family's expectations and the larger community. His is a story about how a child with relentless curiosity forged an identity.

First, Lloyd was a good (mostly) Jewish boy. The title of the book references his weekends at aged 8 years, when he went with his dad to the small stationery store the family owned and would put together the *New York Times*, *Daily News*, and the *Herald Tribune* for customers who would stream in that Sunday. The ink from the papers would stain his hands, face, and clothes, and the experience rubbed off on him indelibly. He often wished he were somewhere else and became determined to be someone else. In this, his family—

particularly his dad—supported his journey.

Second, Lloyd was a very funny boy—with a very Jewish sense of humor (ie, like Neil Simon or Mel Brooks). When it came time for him to learn an instrument, he picked the accordion. The accordion! Complicated, with bellows (“that could fan Hades”), he played it in school orchestra. His Bar Mitzvah was not a typical rite of passage. Although he went to Hebrew school and learned his Torah portion, he would have preferred shooting hoops in the playground. Mesmerized by firecrackers in the neighborhood, he bought some from older boys and resold them (can you be a firecracker pusher?) to his fellow Hebrew school students just before Hebrew school, making a tidy little profit. Busted by the Rabbi (which proves to be a hilarious scene in the book), he worries less that his Bar Mitzvah would not happen and more about his dad's reaction. His dad said nothing, implying approval. As he opines, “After all, wasn't I following my dad's Semitic, merchant bloodline, creating a (small) business and making a profit?”

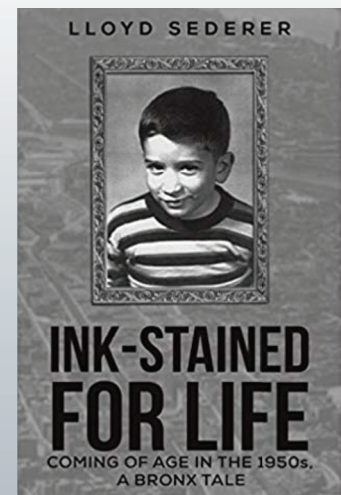
Third, Lloyd was a very lucky boy—and he knows it today. An intact family, not wealthy but with enough. A loving extended family. A safe neighborhood. A rich educational table, thanks to New York's investment in the '50s and '60s in public education from grade school, to Bronx High School of Science to City College.

He learned life's important lessons. Show up, work hard, and then, most importantly, give back. The book is a thank-you note to his parents, teachers, and friends. It is full of gratitude.

I could personally relate to this memoir, having grown up in a family of small business owners (on Long Island, not the Bronx). Although the ability to relate added pleasure to the experience of reading the book, it was not the source of most of the pleasure.

Psychiatrists, and our patients in particular, will benefit by seeing how one of our most effective leaders developed. Fortunately, this development into a wise leader is documented with great humor.

**Dr Sharfstein** is psychiatrist, former president of the American Psychiatric Association, and the 2007 recipient of the Human Rights Award from the American Psychiatric Association. □



### Ink-Stained for Life

by Lloyd Sederer, MD;  
New York: Austin Macauley  
Publishers, 2020

230 pages • \$27.95  
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# A Psychiatrist Weaving Conceptual and Empirical Work

» Awais Aftab, MD

Kenneth S. Kendler, MD, is the Banks Distinguished Professor of Psychiatry and professor of human genetics at Medical College of Virginia, Virginia Commonwealth University. Kendler received his medical and psychiatric training at Stanford and Yale University, respectively. Since 1983, he has been engaged in researching the genetics of psychiatric and substance use disorders. He has utilized methods ranging from family studies to large-sample population-based twin and adoption studies to molecular genetic studies, including linkage, genome-wide association studies, and whole genome sequence aimed at identifying specific genes that influence the vulnerability to a variety of psychiatric disorders. Since 1996, he has served as director of the Virginia Institute of Psychiatric and Behavioral Genetics. Kendler has received numerous national and international awards and is an editor of the journal *Psychological Medicine*. He played an active role in developing DSM-III-R, DSM-IV, and DSM-5 (for which he chaired the Scientific Review Committee), and he is currently the vice-chair of the American Psychiatric Association DSM Steering Committee. He has published more than 1200 articles. Dr Kendler is one of the highest-cited researchers in psychiatry: according to Google Scholar, his academic work has been cited nearly 170,000 times, and his H-index is 196.

Although Dr Kendler is internationally renowned and highly respected for his work in psychiatric genetics, he has been further catapulted into fame over the past 2 decades through his widely read commentaries on the philosophical foundations of psychiatry. I recently had the pleasure of reading the book *Toward a Philosophical Approach to Psychiatry: The Writings of Kenneth Kendler*. The book is a selection of 21 of his most important philosophical and historical papers published throughout his career, addressing topics such as the classification and nature of mental disorders, mind-body relationship, causality and explanation in psychiatry, and historical studies in psychiatric nosology. My admiration of Kendler is no secret at this point.

**AFTAB:** I really like your description of how psychiatric nosology sits in a historically contingent developmental arc. How is this history relevant to ongoing nosological debates in psychiatry, and how has ignorance of this history impeded our efforts at making progress?

**KENDLER:** With respect to psychiatric nosology, there is quite a bit of truth to 2 worn maxims: (1) If you don't know where you have been it is hard to see where you are going, and (2) if you don't know your history, you're at high risk to repeat your prior mistakes. So, I think history can provide a context and a background for what nosology can do and where it has taken wrong roads in the past.

**AFTAB:** I read that you collaborated with a translator to obtain English translations of Kraepelin's previously untranslated works. Will these translations be published or see the day of light in some manner?

**KENDLER:** They are all sitting on my hard drive, and that of the translator Ms Astrid Klee, but there is a lot more there than just Kraepelin. A very small percentage of the relevant German psychiatric literature of the late 19th and early 20th centuries have been translated. I have thought about trying to set up a website to make these widely available.

That will take time, energy, and a bit of resources. If any of these readers want to help, be in touch.

**AFTAB:** You have argued for a scientific pluralism where there are multiple explanatory perspectives available to us to understand psychiatric disorders, and one perspective cannot be reduced to another perspective. You describe your pluralism as empirical and hard-nosed, by which you mean that risk factors must earn their place at the table. It is a little unfortunate that many discussions of pluralism in psychiatry tend to get stuck in debating the merits and demerits of the biopsychosocial model. For the most part, you have managed to stay away from those controversies and have successfully charted a course for pluralism independent of any baggage that the biopsychosocial model brings. Is it time for our field to abandon the biopsychosocial model?

**KENDLER:** Its core idea was on target, but its implementation was so non-specific as to blunt any rigor it might have once had and its ultimate utility. I would not mourn its passing, but it did some important historical work.

**AFTAB:** DSM-5 defines *mental disorder* as a syndrome that, among other things, "reflects a dysfunction in the psychological, biological, or devel-

opmental processes underlying mental functioning." What is the intended meaning of the term *dysfunction*? Did the members of the DSM committee have any clarity or consensus regarding what it means?

**KENDLER:** The hope that we could have a crisp set of inclusion and exclusion criteria for what constitutes a psychiatric dysfunction is a wonderful idea but (in my view, not for lack of trying) impossible. There are too many social and conceptual nuances. So, although there is a general idea of what dysfunction means, operationalizing in the way that would give substantial sharp precision to the definition has not proved possible.

**AFTAB:** Could you articulate what that general idea of dysfunction is? I am also interested in whether *dysfunction* necessarily implies that the locus of the problem is primarily inside the individual and not in interpersonal relations and social context? And, if there is such an implication, does this relegate interpersonal and social causal risk factors to a more secondary status?

**KENDLER:** The general idea of dysfunction is commonsensical—that the relevant psychobiological system is not doing what it is supposed to do. Examples might include providing your higher centers with an

approximately veridical sense of the world around you, keeping levels of anxiety roughly appropriate to the real dangers being confronted, producing mood states approximately congruent to the environmental situation, etc. The DSMs have traditionally seen disorders as existing within individuals and, for example, avoided providing diagnoses for dysfunctional marriages or families. So, in that sense, the underlying disturbance is seen to exist within individuals. I do not see that definition having much of anything to do with the causes. Environmental experiences like severe childhood sexual abuse can clearly cause dysfunctional mood-modulation systems as well as a high genetic vulnerability.

**AFTAB:** To what extent is the dappled distribution of causal risk factors of psychiatric disorders a result of the heterogeneity of constructs? For example, a discussion of the distribution of causal risk factors of *chronic fever disorder* is not likely to be very meaningful. Furthermore, it is true for major depressive disorder as a category that no single causal risk factor has dominant explanatory power, but it may be the case for specific individuals with depression that there are causal risk factors of large explanatory power. What are your thoughts?

**KENDLER:** I don't buy it. Most psychiatric disorders are, I think, multifactorial all the way down. I also think that for a few affected individuals they do suffer from disorders largely as a result of one major cause. I sometimes call your model the *mental handicap model*. Imagine you were a physician in the mid-19th century caring for what would then have been called idiots or imbeciles. If you could apply modern diagnostic methods to that group, a fair proportion would have a range of specific causes: Down syndrome, fragile X, a host of autosomal recessive disorders impacting on all kinds of brain-relevant genes that, when mutated, produce widespread central nervous system dysfunction, a range of small deletions, and a whole bunch would be nonspecific multifactorial. That is, a lot of your cases (but far from all) would have largely monocausal conditions. This has been long postulated for psychiatric illness. It has, in my judgment, been largely a pipe dream. I think that lesson applies more broadly.

**AFTAB:** Your philosophical writings are published and featured promi-

nently in leading American psychiatric journals, which do not usually publish articles related to philosophy of psychiatry. I have wondered if one of the reasons mainstream journals are so receptive to your philosophical work—aside from the undisputed academic quality and rigor—is that your conclusions do not threaten or destabilize the status quo in a way that conclusions of some of the other philosophical commentators do. It was interesting to me that one of your more controversial articles—on the dopamine hypothesis of schizophrenia—was also the one that had a difficult time getting accepted. Why are leading American psychiatry journals publishing so few philosophical articles and so afraid of controversy?

**KENDLER:** I have made a deliberate attempt over the past 15-plus years to try to crack open the leading psychiatric journals for articles with a primary philosophical and/or historical content.

I agree with you that my ability to do that has been, in part, a result of the fact that I have achieved some standing in empirical areas of psychiatric research. To be vernacular, I have accumulated some street cred. I also think the papers were written in a way the audience could understand and that spoke to their concerns. I did not consciously edit the papers to make them less controversial. I still think that nonscholarly issues impacted on the problems we had with the dopamine hypothesis paper—that was perhaps a special case. I do not want to blow up psychiatry. I believe quite deeply in our clinical and research mission, but we surely can think more clearly about a number of issues in our clinical work, nosology and research.

**AFTAB:** Some critics hold the view that if a classification can be misused, it will be misused. To what extent should the concern for misuse constrain classification decisions? Do the creators of DSM have a responsibility to make academic as well as public educational efforts to reduce the ways in which the diagnostic manual is misunderstood and misused?

**KENDLER:** Our primary responsibility on DSM is to our patients and the research community that we assist. But possible misuse does, appropriately, arise in nosologic debates. For example, it played a key role in the opposition to the late-luteal-phase dysphoric debate in DSM-IV—that the diagnoses would be used in ways

prejudicial to women. So, it would be unrealistic for DSM to ignore completely the possible misuse of the document. But, if the chips are down, I think serving our patients and research is the more important mission. It is impossible to control all the possible misuses of DSM and, if you took that concern too far, it would be paralyzing.

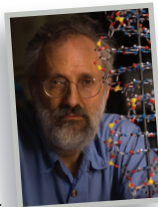
**AFTAB:** You have argued persuasively that the conditions we call *psychiatric disorders* are not merely constructed by individuals and cultures, and that these conditions have some basis in the objective reality, but what do you say about the construct of mental disorder itself? To what extent are concepts of health and disease, and characterizations of disorder grounded in objective reality?

**KENDLER:** As an aggregate concept, I think psychiatric illness (or mental illness) is a real thing out in the world. Going from that to specific disorders, be it schizophrenia or narcissistic personality disorder, that is harder, and the role of social construction or historical accident becomes greater. A metaphor (not my own) is to imagine rewinding the tape of history, say, to 20 centuries BCE and re-running it 100 times until society and medicine developed enough to establish something like what we call psychiatry. I would bet that some construct like insanity/schizophrenia would be there almost all the time. I would not say that for a number of more specific disorders in our manual.

**AFTAB:** You have stated that psychiatric disorders are multicausal, similar to how coronary artery disease, hypertension, and type 2 diabetes are multicausal in medicine. Multifactorial disorders can still have final common pathways onto which those risk factors converge, and those final common pathways provide a lot of explanatory power.

For example, multiple causal risk factors for diabetes converge onto insulin production or insulin resistance. Do you imagine that various causal risk factors for psychiatric disorders also converge onto final common pathways? If it turns out that psychiatric disorders are more like homeostatic property clusters, then it may very well be the case that there may be no final common pathway. In that situation would it still be fair to say that psychiatric disorders are multicausal in the same way as diabetes mellitus is?

**KENDLER:** Great question and topical. I have been involved with a research team trying to determine the biological coherence of the signals emerging from genome-wide association studies. This is a question rather closely related to the one you pose. I guess my main answer is “I hope so.” As you note, that is the case for lots of other complex disorders. To be a bit more precise, I think it is realistic that our “big” syndromes (eg, schizophrenia, alcohol use disorder, depression, anxiety disorders) reflect broad syndromes with some meaningful subtypes within them for which different therapies might have different success. It is awfully optimistic to think that all of them go through one tight final common pathway at which an intervention, properly designed, could be nearly curative for all cases. But similarly, the idea that there are hundreds of kinds of each disorder, each with its own needed therapy, is both very pessimistic and likely unrealistic.



The hope that we could have a crisp set of inclusion and exclusion criteria for what constitutes a psychiatric dysfunction is a wonderful idea... but impossible.

**AFTAB:** You may not remember during the 2016 American Psychiatric Association Annual Meeting, I approached you nervously after a session to express my admiration of your philosophical work. I was a second-year resident at that time. You gave me advice that was something along the lines of “It is very important that you read a lot and that you read very widely.” That often comes to my mind because every day I discover that there is so much more to learn. I am impressed by how you have managed to apply ideas from other areas of philosophy of science to psychiatry. Given that you have limited time, how do you prioritize and decide what you will read?

**KENDLER:** There is never enough time to read everything of interest; I often think of the metaphor of trying to drink a waterfall. I am rather disciplined in what I read. I am good at skimming, and if the first 20 pages don't look good, then I bail. The older I have gotten, the less patient I am with philosophical books written for other professional philosophers, filled with philosophy-speak. If they are not interested in communicating with me, I have to be very, very interested in what they are saying to soldier on.

I read 5 or 6 books at once. I am now reading about the history of genetics and cannot get enough of it. I read very little fiction. But I do keep up other lines of reading, usually late at night, that help keep me rounded, or listen to Audible when I bike or commute. Recently, I have been reading more history of psychiatry than philosophy. I have lots of bookshelves at my home and work office, but I am running out of space.

**AFTAB:** This may be an unfair question: If posterity could remember you predominantly for either your research work in psychiatric genetics or your philosophical work in psychiatry, what would you prefer it to be?

**KENDLER:** I have to laugh—yes unfair—Sophie's choice that I cannot answer. I hope I am remembered, if at all, as someone who has tried to weave together empirical and conceptual work. It has been a wonderful career, and the older I get, the harder it is to pull these 2 parts of what I do apart. My identity is with the whole of it.

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# Neuropsychiatry

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## Neuropsychiatric Symptoms of Multiple Sclerosis

Rajesh R Tampi, MD, MS, DFAPA, DFAAGP, Deena J. Tampi, MSN, MBA-HCA, RN, DFAAGP, and Lori Pittinger, MD

**M**ultiple sclerosis (MS) is the most common inflammatory disease of the central nervous system (CNS).<sup>1</sup> Additionally, it is the most frequent demyelinating disease of the CNS among individuals of European heritage.<sup>2</sup> MS is also recognized as the most common nontraumatic cause of disability due to neurological disease among young and middle-aged adults in Europe and North America.

The prevalence of MS appears to be increasing and is now considered a truly global problem.<sup>3</sup> The prevalence of MS is highest in North America, Western Europe, and Australasia (>100 cases per 100,000 population), whereas it is the lowest in eastern sub-Saharan Africa, central sub-Saharan African, and Oceania (<4 cases per 100,000 population). It is estimated that more than 2 million individuals worldwide have the illness, including approximately 400,000 cases in the United States.<sup>1</sup>

There are several risk factors for MS, one of which is female sex, as approximately three-fourths of the individuals with MS are women.<sup>1</sup> First-degree relatives have a 2% to 4% risk of developing MS

when compared with approximately a 0.1% risk among the general population. The concordance rates among monozygotic twins is approximately 30% to 50%. The genome-wide association studies have identified HLA DRB1\*1501 haplotype as the most important gene variant that increases the risk for developing MS; it confers 3 times the risk for MS. Other risk factors include being from a temperate climate, exposure to tobacco, obesity, and a previous episode of infectious mononucleosis.

There are 4 major categories of MS based on the clinical course of the illness.<sup>4</sup> Relapsing-remitting type of MS (RRMS) affects approximately 85% of individuals with MS; patients with RRMS experience flare-ups (ie, relapses or exacerbation that are followed by periods of remission). In the secondary progressive type of MS (SPMS), the illness course continues to worsen with or without periods of remission or stabilization of symptoms (plateaus). Approximately 10% of patients with MS have the primary progressive type of MS (PPMS), in which the symptoms continue to worsen gradually from the onset of illness. In this form of the

illness, plateaus may be seen but there are no relapses or remissions. Finally, up to 5% of individuals experience the progressive-relapsing type of MS (PRMS). Patients with PRMS have intermittent flare-ups or worsening symptoms with no periods of remission from the onset of illness.

The pathological hallmarks of MS are inflammation with demyelination and astroglial proliferation (gliosis) and neurodegeneration. The damage to tissues is restricted to the CNS, whereas the peripheral nervous system is spared.<sup>5</sup> The 2 pathologies are present among all individuals with MS across the continuum of the disease. Although MS can affect any part of the CNS, the white matter tracts in the cerebral hemispheres, optic nerves, brainstem, cerebellum, and the spinal cord tend to be preferentially affected.<sup>2</sup>

The clinical features of MS depend on the location of the demyelinating lesions in the CNS. In approximately 85% of the cases, the onset of the illness is characterized by an initial clinical attack, which consists of demyelinating lesions in the optic nerve, spinal cord, brainstem, or the cerebellum.

### ACTIVITY GOAL

The goal of this activity is to learn about the neuropsychiatric symptoms of multiple sclerosis (MS) and to recognize them in patients.



### LEARNING OBJECTIVES

1. Appreciate the basic epidemiology of MS
2. Understand the prevalence of comorbid neuropsychiatric disorders and MS
3. Track the complex relationship between MS and the various psychiatric disorders and symptomatology
4. Consider treatment strategies for patients with MS who present with neuropsychiatric disorders

### TARGET AUDIENCE

This continuing medical education (CME) activity is intended for psychiatrists, psychologists, primary care physicians, physician assistants, nurse practitioners, and other health care professionals who seek to improve their care for patients with mental health disorders.

### ACCREDITATION/CREDIT DESIGNATION/FINANCIAL SUPPORT

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lum. This results in acute unilateral optic neuritis, a partial myelitis, or a brainstem syndrome.<sup>6,7</sup> The initial attack may be followed by additional clinical episodes known as relapses. These attacks may have acute or subacute onset over hours to days, with maximal deficits within 4 weeks of onset and spontaneous remission.

### Neuropsychiatric Symptoms

Available evidence indicates that neuropsychiatric symptoms are not uncommon among individuals with MS.<sup>8</sup> Current evidence indicates that approximately 60% of the individuals with MS present with neuropsychiatric symptoms.<sup>9</sup> It has also been noted that in a minority of the cases (2.3%), neuropsychiatric symptoms may present at the onset of the illness, and the burden of these symptoms may remain over the course of illness.<sup>10</sup> Additionally, these symptoms may occur without any other physical manifestations of the illness.<sup>11</sup>

Although there may be overlap, neuropsychiatric symptoms of MS can be divided into 2 broad categories: those associated with cognition and those associated with mood, affect, and behavior.<sup>2</sup> In 1 study, depressive symptoms were the most common neuropsychiatric symptom seen among individuals with MS (**Figure 1**).<sup>12</sup>

### Major Depressive Disorder

Major depressive disorder (MDD) is the most common neuropsychiatric disorder seen among individuals with MS.<sup>9</sup> The lifetime prevalence of MDD is approximately 25% to 50%, which is approximately 2 to 5 times more common than in the general population.<sup>13</sup> As there is significant overlap in symptoms between MDD and MS (including fatigue, reduced appetite, poor concentration, memory deficits, and insomnia), a diagnosis of MDD can often be missed in these individuals.<sup>9</sup> The most commonly observed symptoms among individuals with MS and MDD are persistent low mood, anhedonia, diurnal mood variation, pessimistic thoughts, suicidal ideation, and impaired functioning that is out of proportion to the associated physical disability from the MS. Symptoms like apathy, social withdrawal, feelings of worthlessness, guilt, and poor self-esteem are less likely to be seen.

The relationship between MDD and MS remains a very complex issue.<sup>14</sup> Available evidence indicates that both biological and psychosocial factors play a role in the development of MDD among individuals with MS.<sup>2</sup> It is still unclear whether MDD occurs due to the neuropathological process associated with MS and/or as a consequence of the psychosocial stress associated with being diagnosed with MS.<sup>9</sup>

Biological factors that contribute to the development of MDD among individuals with MS include lesions in the left arcuate fasciculus, prefrontal cortex, anterior temporal lobe, and parietal lobe.<sup>13</sup> Additionally, atrophy in the frontal, parietal, and occipital lobes is associated with the development of depression among individuals with MS. Neuroendocrine factors like hypothalamus-pituitary-adrenal axis dysfunction has been noted among individuals with MS who have MDD. These individuals have non-suppression of cortisol when administered the dexamethasone suppression test, and this finding is correlated with greater number of lesions

in the brain.<sup>15</sup> The use or sudden discontinuation of corticosteroids, baclofen, dantrolene, and tizanidine among individuals with MS increases the risk for MDD.<sup>9</sup> Although there is no clear association noted between the use of interferon and the development of MDD among individuals with MS, patients receiving interferon should be routinely screened for the development of MDD.<sup>15</sup> Interestingly, depression severity has been found to be higher among individuals with MS who use escape-avoidance and emotional respite coping strategies, and less severe among individuals who use planful problem-solving and cognitive reframing.<sup>16</sup>

Suicidal ideation is not uncommon among individuals with MS. One study showed that the lifetime prevalence of suicidal intent was 28.6% in individuals with MS, and 6.4% of individuals with MS had attempted suicide.<sup>17</sup> In this study, suicide intent was strongly associated with major depression, alcohol abuse, and social isolation.

Available evidence indicates that MDD in MS is often poorly diagnosed and treated, with as many as two-thirds of patients not receiving appropriate depression treatment.<sup>9</sup> Screening tools such as the Beck Depression Inventory, the Beck Fast Screen for Depression in Medically Ill Patients, and the Hospital Anxiety and Depression Scale have been successfully used for screening in this patient population. Although there are only a limited number of controlled studies, available evidence indicates the following for the treatment of MDD among individuals with MS: selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressant (TCAs), mirtazapine, selective serotonin and noradrenergic reuptake inhibitors (SNRIs), and bupropion.<sup>18</sup> Electroconvulsive therapy has also been used for the treatment of MDD among individuals with MS with good efficacy and minimal adverse effects.

The good news is appropriate treatment can be helpful for these patients. In a meta-analysis, Fiest et al found 21 articles that reported data on 13 unique clinical trials for the treatment of depression in MS.<sup>19</sup> The investigators found that depression severity improved in 9 psychological and 3 pharmacological trials of treatments for depression.

### Bipolar Disorder

The prevalence of bipolar disorder among individuals with MS is 0.3%.<sup>20</sup> When compared with con-

trols, individuals with MS had greater lifetime prevalence of bipolar I disorder ( $P = .05$ ), bipolar 2 disorder ( $P < .0001$ ), and cyclothymia ( $P = .0001$ ).<sup>21</sup> Manic symptoms can either precede the occurrence of neurological symptoms of MS or may occur during the exacerbation of MS symptoms.<sup>15</sup> One-third of individuals with MS experience drug-induced mania, which tends to occur early in treatment and is dose dependent.<sup>9</sup> Manic symptoms also occur more commonly among individuals with a family history of bipolar disorder. Additionally, manic symptoms may be seen among individuals with greater volume of brain lesions, especially in the bilateral temporal horn.<sup>22</sup>

Lithium has been found to be effective in the treatment of manic symptoms among individuals with MS. For drug-induced manic symptoms, lithium, olanzapine, and phenytoin are effective treatments.<sup>9</sup> Symptom control can be achieved without reduction in doses of the offending drug.

### Anxiety Disorders

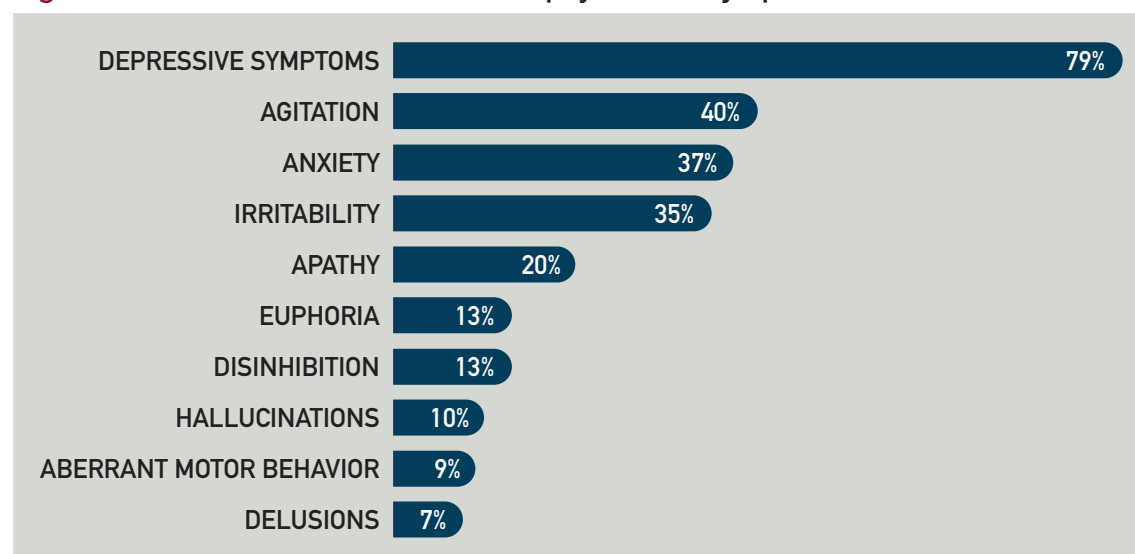
Available evidence indicates the prevalence rate for anxiety disorders among individuals with MS is approximately 36% (**Figure 2**).<sup>23</sup> Individuals with anxiety disorders were more likely to be women, have a history of depression, drink alcohol to excess, report higher social stressors, and have contemplated suicide. In a majority of these cases, the diagnosis of an anxiety disorder had been missed, and therefore they had not received any treatment.

There are no RCTs that have evaluated pharmacotherapy for anxiety disorders among individuals with MS, but available evidence indicates efficacy for SSRIs, SNRIs, pregabalin, gabapentin, and beta-blockers.<sup>9</sup> The use of benzodiazepines should be restricted to cases of anxiety that are acute and severe, and the prescription should be only be given for a short duration of treatment. Nonpharmacological management strategies that are beneficial in cases of anxiety disorders in MS include stress management and cognitive behavioral therapy.

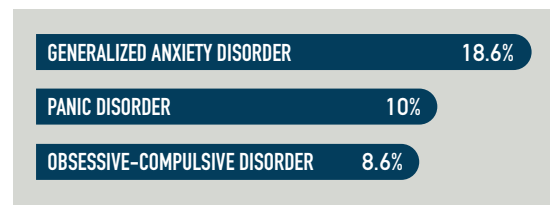
### Psychotic Disorders

Psychotic symptoms are seen in approximately 2% to 4% of individuals with MS.<sup>24</sup> This rate is 2 to 3 times than that among the general population. It has also been noted that in 90% of these cases, psychotic symptoms occur in individuals after the

**Figure 1. Prevalence of Common Neuropsychiatric Symptoms in MS**



**Figure 2. Prevalence and Types of Anxiety Disorders in MS**



onset of symptoms of MS.<sup>9</sup> A systematic review found that the mean age of individuals having psychotic symptoms was 34.4 years, and there was a female predominance.<sup>25</sup> In the majority of cases, the individuals did not have a prior history of psychiatric disease. Additionally, a majority of cases could be classified as a psychotic disorder or a mood disorder with psychotic features.

In this review, most of the individuals received some type of antipsychotic medication, with variable success. About a quarter of these individuals were treated with corticosteroids in the acute phase of their psychotic symptoms, and the majority responded favorably. In the 60% of individuals with imaging data, predominantly frontotemporal lesions were noted; most had contrast enhancing lesions. Data available from these case reports indicate that hallucinations and delusions (mostly paranoid) were the most common symptom, followed by irritability/agitation, sleep disturbance, grandiosity, and several others (Figure 3).<sup>24</sup>

Psychotic symptoms are thought to occur in individuals with MS via 3 mechanisms: through a shared common pathophysiological process with the MS; due to the regional demyelination that occurs in synchrony with the course of MS; and as a side effect or as an exacerbation of the effect of the medications used to treat MS.

Available evidence indicates efficacy for low-dose atypical antipsychotic agents, including risperidone, ziprasidone, clozapine, aripiprazole, quetiapine, and olanzapine.<sup>9</sup> Clozapine is often prescribed for treatment-resistant psychosis due to the risk for agranulocytosis. Prophylactic use of lithium along with corticosteroids and low doses of chlorpromazine have also shown benefit in the treatment of psychotic symptoms in MS.<sup>13</sup>

### Substance Use Disorders

Estimates show 19% of individuals with MS have misused psychoactive substances or alcohol within the past month.<sup>26</sup> Substance use tends to occur more commonly among younger individuals, those individuals who are still employed, and among those individuals who have less severe symptoms.<sup>27</sup> One study found that 43% of individuals with MS had used cannabis at some time during the illness.<sup>28</sup> Of these, 68% of individuals had used cannabis to alleviate symptoms of MS. A total of 18% of the individuals had used cannabis in the last month, of whom 12% had used it for symptom relief. Being married or having a long-term partner, smoking tobacco, and increasing disability were independent risk factors for MS-related cannabis use. When compared with individuals who could walk unaided, cannabis use was more likely in those who were chair-bound (adjusted odds ratio [OR]=2.47) or only able to walk with an aid (adjusted OR=1.56). Pain and spasms were common reasons for cannabis use. Interest-

ingly, 71% of individuals with MS who had never used cannabis said they would try the drug if it were available on prescription.

Unfortunately, the use of cannabis is associated with a number of adverse effects, including worsening cognitive functioning, worsening depressive symptoms, and/or psychosis.<sup>9</sup> It is important to routinely screen for alcohol and/or psychoactive substance misuse among individuals with MS and, if present, refer these individuals for appropriate treatments.<sup>15</sup>

### Cognitive Disorders

Evidence shows that 40% to 65% of individuals with MS have cognitive dysfunction.<sup>29</sup> These individuals present with impairments in attention and information processing along with deficits in working, semantic, and episodic memory.<sup>30</sup> Procedural and implicit memory, however, appear less impaired among individuals with MS. Patients also present with deficits in encoding memory when compared with retrieval functions. Additionally, these individuals have executive dysfunction, including deficits in concept formation, abstract reasoning, and verbal fluency. Cognitive impairment tends to occur early in the illness and tend to worsen as the illness progresses. Those individuals with RRMS do better than individuals with PPMS with regards to cognition.

There is a possible association noted between cognitive dysfunction and fatigue.<sup>29</sup> Fatigue often impairs cognitive performance among individuals with MS, and cognitive dysfunction may increase fatigue levels. Fatigue and cognitive dysfunction appear to share a common pathophysiological substrate involving common frontal-subcortical pathways. It has been noted that the total lesion burden and regional lesion volume correlate with the extent of cognitive dysfunction.<sup>30</sup> Ventricular enlargement that is correlated with cerebral atrophy is also associated with impaired cognitive functioning, especially in attention, verbal memory, and verbal fluency.

The most sensitive means to detect cognitive dysfunction among individuals with MS is neuropsychological testing. Unfortunately, the testing is time consuming, expensive, and not readily available. In such situations, brief screening instruments, such as the Minimal Assessment of Cognitive Function in MS, may be used to detect and

monitor for the progression of cognitive impairment. Disease-modifying drugs, including beta-interferons and glatiramer acetate, may prevent or reduce the progression of cognitive dysfunction by containing the development of new cerebral lesions.<sup>31</sup> However, clinical trials have provided inconsistent results, with neuropsychological effects documented only in 1 trial.

Pilot studies have tested symptomatic therapies for fatigue, which may share a common pathophysiological substrate with cognitive dysfunction. Small trials of amantadine, pemoline, 4-aminopyridine, and 3-4 aminopyridine have provided mainly negative results.<sup>31</sup> Acetylcholinesterase inhibitors (AChEIs) used to treat Alzheimer disease—such as donepezil, rivastigmine, and galantamine—have recently been explored for individuals with MS, with the majority of pilot trials showing promising results.<sup>32</sup> However, nonpharmacological interventions based on cognitive rehabilitation in general have provided limited results.<sup>33</sup>

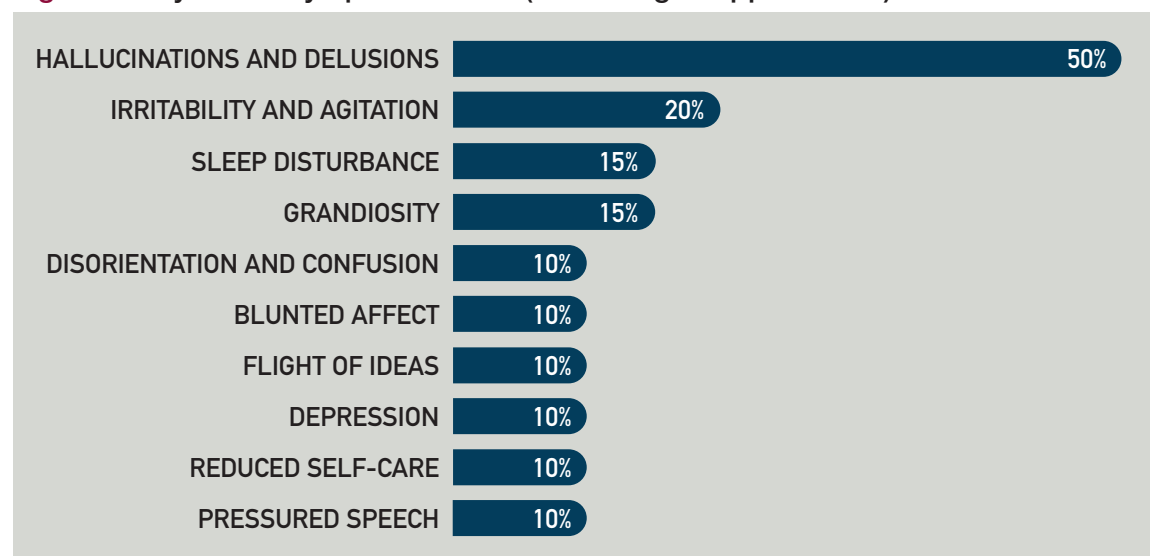
### Pseudobulbar Affect

Pseudobulbar affect (PBA) is seen in approximately 10% of individuals with MS.<sup>9</sup> Individuals with PBA appear to have greater physical disability and are more likely to be in the chronic progressive stage of MS.<sup>15</sup>

PBA, also known as pathological laughing and crying, emotional incontinence, pathological emotionalism, or involuntary emotional expression disorder, is considered a disconnection syndrome that results in the loss of cortical or brainstem inhibition of a putative center for laughing and crying.<sup>9</sup> Additionally, lesions in the brainstem and inferior frontal and parietal lobes, along with the involvement of the monoaminergic neurotransmitter systems, have been noted in individuals with PBA. PBA can be distinguished from a mood disorder by the dissociation between the affect and the underlying mood, which results in an incongruent emotional expression. This emotional expression is disproportionate to the underlying emotional experience. In addition, these symptoms are not associated with the neurovegetative symptoms associated with mood disorders, and they do not meet the duration criteria for the mood disorders.

The self-report Center for Neurologic Study-Lability Scale is often used to screen for PBA.<sup>34</sup> A combination of dextromethorphan and quinidine is

**Figure 3. Psychosis Symptoms in MS (Percentages Approximate)**



approved by US Food and Drug Administration (FDA) for the treatment of PBA. Symptoms of PBA also respond rapidly to low therapeutic doses of SSRIs. Efficacy has also been noted for SNRIs, mirtazapine, TCAs, levodopa, amantadine, and lamotrigine in the treatment of PBA.<sup>9</sup>

### Concluding Thoughts

Neuropsychiatric symptoms are not uncommon among individuals with MS. Although these symptoms may occur prior to the onset of MS symptoms, they commonly occur during the course of the illness. It is still unclear if the occurrence of neuropsychiatric symptoms indicates the level of severity of the underlying illness. However, the presence of these symptoms worsens MS outcomes. The management of the neuropsychiatric symptoms among individuals with MS includes the optimal use of standard psychotropic medication regimen in conjunction with disease-modifying agents that are used to treat symptoms of MS. In addition, the use of appropriate psychotherapeutic interventions improves outcomes among these individuals. Ideally, neuropsychiatric symptoms in MS should be managed by a psychiatrist and a neurologist, with active collaboration between the providers and optimization of available services to care for these individuals.

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clerkship site director, Cleveland Clinic Akron General, Akron, Ohio; clinical experiential director, Psychiatry Clerkship, Northeast Ohio Medical University, Rootstown, Ohio; clinical associate professor of psychiatry, Northeast Ohio Medical University, Rootstown, Ohio.

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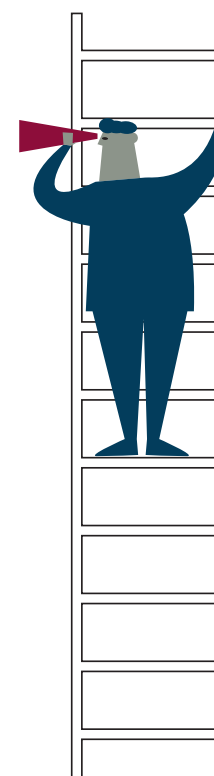


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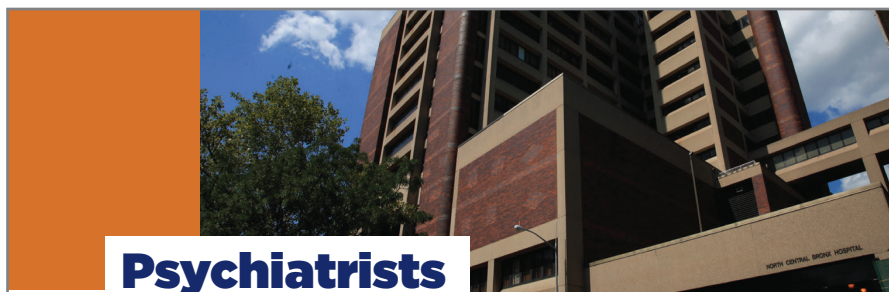
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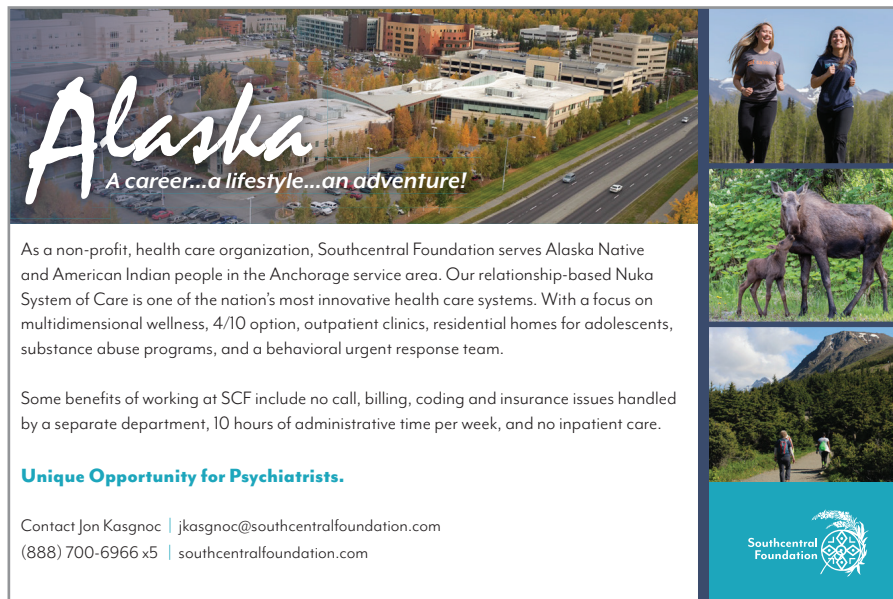
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Take the first step in joining one of our teams and contact **Blair Eversley** at **(916) 538-3948** or [CentralizedHiringUnit@cdcr.ca.gov](mailto:CentralizedHiringUnit@cdcr.ca.gov). You may also apply online at [www.cchcs.ca.gov](http://www.cchcs.ca.gov).





Hackensack  
Meridian Health



Hackensack  
Meridian Health



SETON HALL  
UNIVERSITY

HACKENSACK MERIDIAN SCHOOL OF MEDICINE  
AT SETON HALL UNIVERSITY

## Department of Psychiatry

*With the continued growth of our Department of Psychiatry and our New General Psychiatry Residency Programs at Ocean Medical Center and Jersey Shore University Medical Center our vision for Behavioral Health is Bright.*

**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 -Inpatient Attending-** Child/Adolescent and Adult/Geriatric–Carrier Clinic (Belle Mead, NJ)  
**Carrier Clinic – Inpatient- PT House Physician (weekends)**  
**On-Call Weekend Rounding Physician**
- **Child & Adolescent Section Chief** – Includes Pediatric CL: Jersey Shore University Medical Center, (Neptune, NJ)
- **Consultation Liaison Psychiatrists:** Hackensack University Medical Center (Hackensack, NJ), JFK Medical Center (Edison, NJ), Ocean Medical Center (Brick, NJ), Jersey Shore University Medical Center (Neptune, NJ)
- **Outpatient:** Ocean Medical Center (Brick, NJ)
- **Staff Psychiatrist for Adult Inpatient Unit:** Riverview Medical Center (Red Bank, NJ) and Hackensack University Medical Center (Hackensack, NJ)
- **Outpatient Child & Adolescent Psychiatrist:** Hackensack University Medical Center (Hackensack, NJ)
- **Geriatric Psychiatry:** Hackensack University Medical Center (Hackensack, NJ)
- **ED/Crisis Unit:** Jersey Shore University Medical Center (Neptune, NJ)
- **Telehealth Remote Psychiatrist**

**Renee.Theobald@hackensackmeridian.org or call: 908-839-5693**

## CALIFORNIA



### Full-time psychiatrist for a large public health & hospital system in Silicon Valley

\$275,080 - \$357,600 annually  
36 days of annual leave  
Full benefits & retirement

(Above annual salary includes additional pay for Board Certification and Acute Settings)

Santa Clara Valley Health and Hospital System, a public healthcare system in the heart of Silicon Valley, is seeking full-time BE/BC psychiatrists for a variety of clinical settings, including emergency psychiatric services, inpatient consultation liaison services, jail custody health inpatient services, specialty mental health outpatient services and primary care behavioral health services.

As the largest public health care system in northern California, we offer comprehensive healthcare resources to a large and diverse patient population. Psychiatrists are part of a robust team of staff that work in collaboration with other medical specialties and behavioral health clinicians to provide integrated health care to patients.

Psychiatrists are eligible for numerous benefits including 36 days of annual leave, 5 days of educational leave, 12 holidays, \$4500 educational funds, health benefits, life insurance and CalPERS retirement plan. No calls required.

In addition, part-time opportunities for BE/BC psychiatrists, PGY IIIs and IVs are available.

If you are interested in working in a dynamic and collegial work environment, please submit a CV and letter of interest to MD.Recruitment@hhs.sccgov.org.

The County of Santa Clara is an Equal Opportunity Employer



SAN JOAQUIN COUNTY  
CALIFORNIA  
Greatness grows here.

### Outpatient Psychiatry Opportunity

San Joaquin County Behavioral Health Services is seeking to fill Outpatient Adult [General], and Sub-Specialty Psychiatry (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; comprehensive 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@sjcbhs.org. EOE



### Psychiatrist Position Excellent Opportunity in California

Imperial County Behavioral Health Services is currently recruiting for full-time or part-time psychiatrists. Imperial County, a rich farming area with a population of 180,000, is located 90 miles east of San Diego, 90 miles south of Palm Springs, 60 miles west of Yuma, Arizona, and just north of the cosmopolitan city of Mexicali, Mexico. San Diego State University maintains a satellite campus in Calexico, and there are several private and public universities located in Mexicali. Imperial County's location and diversity make it the perfect place for any professional.

The position pays a highly competitive salary, including health benefits for you and your family, requires no hospital work and minimal after-hours work, freeing you up for more leisurely activities. As a Psychiatrist with Imperial County Behavioral Health, you will be part of a multi-disciplinary treatment team that includes therapists, nurses and rehabilitation technicians that provide comprehensive support and resources to assist clients in achieving recovery.

**J-1 and H-1-B Applicants welcome.** Our agency is experienced in successfully processing J-1 Waiver and H-1B Visa applicants.

Qualified candidates must have a CA medical license or ability to obtain. Send CV to Imperial County Behavioral Health Services, 202 North 8th Street, El Centro, CA 92243.

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



HILLVIEW  
MENTAL HEALTH CENTER, INC.

### PSYCHIATRIC NURSE PRACTITIONER

Hillview Mental Health Center, Inc., has an opening for a Psychiatric Nurse Practitioner to work across all our programs. Our multi-disciplinary treatment team provides comprehensive mental health, medication support, targeted case management, and individualized employment support and placement services to individuals aged 18 and older that have identified a mental health barrier to obtaining and/or maintaining employment.

#### Qualifications

- Current Nurse Practitioner Licensure + 2 years' experience as Nurse Practitioner
- Desire to work with adults (aged 18 and older) with a serious mental illness
- Must show valid California driver's license and current automobile insurance prior to start date
- Must maintain a good driving record and provide verification of current automobile insurance on an annual basis.
- Ability to pass thorough background check. Hillview will consider for employment all qualified applicants, include those with criminal histories, in a manner consistent with applicable state and local laws, including City of Los Angeles Fair Chance Initiative for Hiring Ordinance.

#### Required Education

- Graduated from accredited school of nursing, specialty in psychiatric/mental health

#### Preferred Skills

- Bilingual in Spanish-English.
- Experience with substance use treatment and/or specialization in co-occurring disorders.
- Knowledge of Los Angeles County Department of Mental Health records paperwork
- Experience using electronic health records

As a member of the Hillview team, employees enjoy competitive salaries and an excellent benefit package including paid vacation, holidays, credit union, 401(k) plan and medical, dental, life and long-term care insurance paid by Hillview.  
EOE

Please email your resume, cover letter and salary expectation (within the body of the email; please no attachments) to:

jobs@hillviewmhc.org

**CALL  
TODAY**  
**(609) 495-4367**

## DELAWARE



### Psychiatrist Opportunities in Delaware and Maryland!

ChristianaCare, the largest healthcare system in Delaware, is expanding its behavioral health program. We have five position openings for BE/BC psychiatrists working either in Delaware or Maryland.:

- 2 ER/Consult positions (Teaching):
  - Christiana Hospital (906 bed Level 1 Trauma Center), Newark DE
  - Wilmington Hospital (306 beds), Wilmington, DE
- 1 Outpatient Psychiatrist (Teaching)
  - Practice located on the Newark campus, Newark, DE.
- 1 Inpatient (Teaching)
  - 30 bed voluntary unit in the Wilmington Hospital, Wilmington, DE
- 1 Inpatient/Consult Position
  - Union Hospital (72 beds), Elkton, MD. 10 bed inpatient unit.

#### Why ChristianaCare:

- Teaching opportunities with ChristianaCare psychiatry residents and medical students.
- Excellent work life balance with reasonable weekend call
- Base salary; annual bonus, paid weekend call; CME allowance, relocation and generous 403b match and defined contribution plan
- Ability to work some time remotely may be possible
- Our location- On the 1 95 corridor with easy access to Philly, NYC and Washington DC; reasonable cost of living; excellent education, retail and entertainment/sports options; moderate climate; 2 hours to beach and ski resorts.

#### How to Apply:

Contact Amy Bird, Director Provider and Medical Group Recruitment at abird@christianacare.org  
or go to our website at <https://careers.christianacare.org>

## MISSOURI



### PSYCHIATRIST

Provide full-time face-to-face psychiatric services to patients in Raymore, MO for a minimum of 40 hours a week. In addition, may provide services to patients in Royal Oaks Hospital in Windsor, Missouri, as assigned. M.D. or professional equivalent degree, BC/BE in Psychiatry and Missouri medical license required. This position is eligible for the Employee Referral Program. Position is with Compass Health, Inc., d/b/a Pathways Community Health in Clinton, MO. Send C.V. to: Ms. Cathy Grigg, Director of Psychiatry Services at cgrigg@pbhc.org Fax: 417-532-6606.

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to view our  
**extensive list of jobs**

## NEW JERSEY



University Behavioral Health Care

**RUTGERS UBHC is seeking Psychiatrists for Child and Adolescent Inpatient Unit, Adult Inpatient Unit and Acute Psychiatric Services in Piscataway, NJ**

Rutgers UBHC is seeking board eligible or board certified psychiatrists for immediate full time openings at Rutgers University Behavioral Healthcare on the Child and Adolescent Inpatient Unit and the Adult Inpatient Unit/Acute Psychiatric Services.

The psychiatrists will be members of a multidisciplinary team comprised of social workers and nurses; will supervise child psychiatry fellows, general psychiatry residents and medical students; and will have academic appointments at Rutgers Robert Wood Johnson Medical School.

**Successful candidates must be:**

- ABPN board-certified or board-eligible in Psychiatry and Neurology (for adult inpatient)
- ABPN board-certified or board-eligible in Child and Adolescent Psychiatry (for child inpatient)
- NJ licensed or eligible for licensure in NJ
- Able to work as part of a team

**More about the position:**

- Location has nearby community attractions including delicious dining options, theater and other cultural venues.
- Easy access to major metropolitan areas
- Opportunity to work in the inpatient setting
- Comprehensive salary package and benefits
- Attractive compensation for weekend calls (adult services)

**Apply online:**

Psychiatrist for Child & Adolescent Inpatient & Partial Hospitalization: <https://jobs.rutgers.edu/postings/112288>

Psychiatrist for Adult Inpatient Unit and APS: <https://jobs.rutgers.edu/postings/121136>

**Rutgers UBHC has immediate job openings for outpatient psychiatrists and psychiatric mental health nurse practitioners. To apply, email cover letter and curriculum vitae to [ubhc-job-applications@ubhc.rutgers.edu](mailto:ubhc-job-applications@ubhc.rutgers.edu).**

**Our competitive rates can help you promote physician products and services.**



Department of Psychiatry

Transforming Lives Through Research, Clinical Care and Education

## UMass Memorial Health Care and the University of Massachusetts Medical School currently have openings within the Department of Psychiatry.

The Department of Psychiatry is a national leader in public sector psychiatry, child and adolescent psychiatry, neuropsychiatry, biological psychiatry, psychosocial rehabilitation, women's mental health, and addiction psychiatry. 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 particularly interested in having Faculty join our Department who are motivated for a career in clinical research. We are the largest provider of psychiatric services in central Massachusetts, with over 400 faculty members and 12 hospitals and community mental health centers.

Our residency program trains 7 residents per year, including general psychiatry and specialty tracks for combined adult and child psychiatry and combined neurology. We offer fellowships in Child and Adolescent Psychiatry, Addiction Psychiatry, Forensic Psychiatry, Neuropsychiatry, and Adult Developmental Disabilities. Interested candidates should send their curriculum vitae addressed to Dr. Kimberly Yonkers.

### UMass Medical School

#### Facility Medical Director (Cape Cod and Islands Mental Health Center, Pocasset, MA)

Provides administrative and clinical oversight for the DMH-operated and contracted state hospital and community support programs. Clinical Care in our Partial Hospital program.

#### Forensic Psychiatrist (Worcester Recovery Center and Hospital, Worcester, MA) Inpatient Services

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

#### FOR ADDITIONAL INFORMATION, PLEASE CONTACT:

**Marie Hobart, MD, Vice Chair, Public Sector Psychiatry**  
[marie.hobart@umassmed.edu](mailto:marie.hobart@umassmed.edu)

Interested applicants should apply directly at  
<https://academicjobsonline.org/ajo/UMASSMED/Psych>  
(J-1 and H-1B candidates are welcome to apply)

### UMass Memorial Health Care

#### Chief Medical Officer (CHL, Worcester, MA)

Supervision of a large group of professionals and participation in development efforts serving >22,000 individuals each year.

#### General Adult Outpatient Psychiatrist (Worcester, MA) Outpatient services while providing behavioral healthcare services.

#### Medical Director (Adult Inpatient Psychiatry Marlborough, MA) Provide psychiatric and medical supervision and direction to a 22-bed behavioral health unit

Interested applicants should submit a letter of interest and curriculum vitae addressed to Kimberly Yonkers, MD:  
c/o: Jessica Saintelus, Physician Recruiter  
[Jessica.Saintelus@umassmemorial.org](mailto:Jessica.Saintelus@umassmemorial.org)

<http://jobs.jobvite.com/umassmemorialmedicalgroupphysicians/search?q=&d=Psychiatry>

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

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# Drizalma Sprinkle™ Capsules Have Demonstrated Bioequivalence to Cymbalta® [duloxetine delayed-release capsules]<sup>1,4</sup>

**Drizalma Sprinkle™**  
(DULOXETINE) DELAYED-RELEASE CAPSULES  
20 mg, 30 mg, 40 mg, 60 mg



- Because delayed-release duloxetine capsules are not able to be crushed, opened, or sprinkled, Drizalma Sprinkle™ provides the first and only once-daily, delayed-release dosing option for patients who cannot or will not swallow solid medication forms<sup>1,5,6</sup>
- Drizalma Sprinkle™ provides the same drug release whether it is swallowed whole in capsule form, sprinkled over applesauce, or administered via nasogastric tube<sup>1</sup>

The duloxetine your patients require—approved in a sprinkle formulation designed for those who cannot or will not swallow solid forms of medication<sup>1</sup>

## Dosing and Administration



- Drizalma Sprinkle™ is available in 4 dosage strengths—20 mg, 30 mg, 40 mg, and 60 mg—for flexibility and easy titration<sup>1</sup>
- Drizalma Sprinkle™ can be administered with or without food. Capsules can be opened, and the contents sprinkled over applesauce<sup>1</sup>

## IMPORTANT SAFETY INFORMATION [cont'd]

### ADVERSE REACTIONS

The most common adverse reactions ( $\geq 5\%$  and at least twice the incidence of placebo patients) were nausea, dry mouth, somnolence, constipation, decreased appetite, and hyperhidrosis.

### DOSING AND ADMINISTRATION

Drizalma Sprinkle™ may be taken with or without food. Drizalma Sprinkle™ may be swallowed whole (do not crush or chew capsule); opened and sprinkled over applesauce; or administered via nasogastric tube.

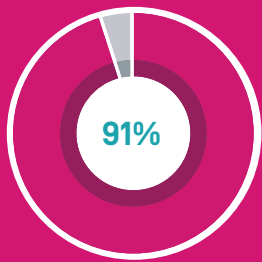
### DRUG INTERACTIONS

- Avoid concomitant use with potent CYP1A2 inhibitors
- Consider dose reduction with concomitant use with CYP2D6 substrates

### USE IN SPECIFIC POPULATIONS

- **Hepatic Impairment:** Avoid use in patients with mild, moderate, or severe hepatic impairment
- **Renal Impairment:** Avoid use in patients with severe renal impairment
- **Pregnancy:** Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during treatment with Drizalma Sprinkle™. Third trimester use may increase risk of symptoms of poor adaptation (respiratory distress, temperature instability, feeding difficulty, hypotonia, tremor, irritability) in the neonate. Advise patients that Drizalma Sprinkle™ use during the month before delivery may lead to an increased risk for postpartum hemorrhage and may increase the risk of neonatal complications requiring prolonged hospitalization, respiratory support and tube feeding

Please see additional Important Safety Information throughout this journal cover wrap, and Brief Summary of Full Prescribing Information, including Boxed Warning.



## Drizalma Sprinkle™ is Covered on Most Medicare Part D Plans

91% of lives on the top 10 Medicare Part D plans are offered coverage for Drizalma Sprinkle™<sup>4</sup>

### Prescribe the Only Formulation of Duloxetine That is Designed to Be Opened and Sprinkled<sup>1</sup>

Drizalma Sprinkle™ is designed for patients who cannot or will not swallow solid medication forms<sup>1</sup>

### Drizalma Sprinkle™ provides effective therapy in one formulation for 4 different indications<sup>1</sup>:

- Major Depressive Disorder (MDD) in adults
- Generalized Anxiety Disorder (GAD) in adults and pediatric patients aged 7 to 17 years
- Diabetic Peripheral Neuropathic Pain (DPNP) in adults
- Chronic musculoskeletal pain in adults



### IMPORTANT SAFETY INFORMATION (cont'd)

#### USE IN SPECIFIC POPULATIONS (cont'd)

- **Lactation:** Advise breastfeeding women using duloxetine to monitor infants for sedation, poor feeding and poor weight gain and to seek medical care if they notice these signs

To report SUSPECTED ADVERSE REACTIONS, contact Sun Pharmaceutical Industries, Inc. at 1-800-818-4555 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

Please see additional Important Safety Information throughout this journal cover wrap, and Brief Summary of Full Prescribing Information, including Boxed Warning.

**To Learn More, Visit: [drizalmasprinklehcp.com](http://drizalmasprinklehcp.com)**

**References:** **1.** Drizalma Sprinkle™ [prescribing information]. Cranbury, NJ: Sun Pharmaceutical Industries, Inc., 2020. **2.** National Alliance on Mental Health. Depression in older persons fact sheet. National Council on Aging website. [www.ncoa.org/wp-content/uploads/Depression\\_Older\\_Persons\\_FactSheet\\_2009.pdf](http://www.ncoa.org/wp-content/uploads/Depression_Older_Persons_FactSheet_2009.pdf). Published October 2009. Accessed October 2, 2020. **3.** Center for Drug Evaluation and Research, US Food and Drug Administration. *Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules: Guidance for Industry*. [www.fda.gov/media/87344/download](http://www.fda.gov/media/87344/download). Published June 2015. Accessed October 2, 2020. **4.** Data on file. Sun Pharmaceutical Industries, Inc., Princeton, NJ. **5.** Institute for Safe Medication Practices. Oral dosage forms that should not be crushed. Published November 1, 2018. Accessed October 2, 2020. [www.ismp.org/recommendations/do-not-crush](http://www.ismp.org/recommendations/do-not-crush). **6.** Cymbalta® [prescribing information]. Indianapolis, IN: Lilly USA, LLC; 2020.

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