Imagine that you, as a physician, just saw this headline splashed all over the internet: “Depression Probably Not Caused by Excessive Black Bile.” It was followed by a long discourse on how an imbalance in the 4 bodily humors is not responsible for mood disorders. You might scratch your head and wonder why anyone in 2022 would be bothering to refute the Galenic-medieval humoral theory. Continued on page 6

Ronald W. Pies, MD; George Dawson, MD

Serotonin or Not, Antidepressants Work

Serotonin: A Biography

Serotonin is a ubiquitous neurotransmitter that has earned its reputation as a highly significant molecule in humans that lies at the center of a diverse range of functions. When Vittorio Erspamer first discovered serotonin—which he initially named enteramine—in 1935, he demonstrated that it was produced by enterochromaffin cells, which are endocrine cells adjacent to the lining of the gastrointestinal tract. When released, enteramine increased motility and secretions of the intestines.

From the Editor John J. Miller, MD

Serotonin: A Biography

Continued on page 4
Publisher's Note

School Is in Session

September always feels like back-to-school season, even though many districts across the country start earlier. The smell of fall is in the air as the kids gather their books and march back to school, some with more enthusiasm than others. Little do they realize the importance of ongoing education and the likely role learning will continue to play in their lives.

As professionals in a dynamic medical field, psychiatrists and psychiatric clinicians recognize this need to continue learn and grow, especially as science progresses. Perhaps that is why the serotonin debate that hit the popular press struck such a chord with readers and contributors alike. In this issue, you will read insights from a former editor in chief and the current one. They discuss the facts and the myths and provide balanced commentaries to keep you up-to-date and confident in your prescribing practices.

No doubt, the onslaught of criticisms against psychiatry can take its toll. This month’s Special Report continues the exploration of physician wellness and burnout prevention. Sometimes the hardest lesson is learning to take care of oneself, especially for those in caring professions. However, the friendly skies provide the cues you should follow: It is important to put the oxygen mask on yourself before assisting others.

School continues to be in session as, from cover to cover, *Psychiatric Times*™ provides you with clinical pearls, data, and practical support aids so you can successfully take care of yourself and your patients.

Mike Hennessy Jr
President and CEO, MJH Life Sciences

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At Cleveland Clinic in 1948, 3 researchers discovered a molecule released by platelets in the blood that facilitated vasovasodilation, helping facilitate blood clotting and decrease blood loss. They named this molecule serotonin, which is Latin for vasosconstrictor. Finally, in 1952, it was confirmed that enteramine and serotonin were the same molecule.

Although it is often referred to as serotonin today, its official chemical name is 5-hydroxytryptamine (5-HT). Serotonin is one of several molecules collectively called monoamines, which also include norepinephrine, dopamine, and histamine.

Serotonin is localized in 3 primary systems in the human body, with 90% of it in the enterochromaffin cells in the gastrointestinal tract, 8% in platelets, and the remaining 2% in the central nervous system. Serotonin’s presence in these 3 diverse body systems tells a powerful story about how this single molecule ultimately integrates disparate systems to increase survival of the organism. If you were to eat a toxic substance, the enterochromaffin cells in your gastrointestinal tract would secrete serotonin, which would then agonize the numerous 5HT-4 receptors throughout the gut, which results in increased gastrointestinal motility/secretions and secretions. The wisdom of the body wants to get that toxic substance out as quickly as possible.

The increased serotonin diffuses into the vasculature where platelets—which cannot synthesize the vasocostricting serotonin on their own—use serotonin transport pumps to fill their serotonin vesicles and remove this excess serotonin from the blood at the same time. However, if that toxic substance raises a red alert, the platelets’ serotonin transport pumps get saturated with serotonin, and the blood serotonin levels rise to an abnormal level. As this blood perfuses the brain, the increased serotonin will agonize the 5HT-3 ionotropic receptors in the chemoreceptor trigger zone, which induces vomiting. The serotonin thus facilitates expulsion of the toxin from both ends of the gastrointestinal tract, increasing the likelihood of surviving the ingestion of this toxin.

This example is a microcosm of the massive macrocosms of circuitry that serotonin orchestrates. Serotonin’s activity in the gastrointestinal tract and platelets is straightforward and well established. When we attempt to understand serotonin’s detailed functioning in the brain, the mountains of information that exist give us a few clues here and there. Ultimately, we are not yet smart enough to map out the system, and all the interfaces serotonergic pathways share with the other neuronal circuits and neurotransmitters.

The brain directs its serotonergic pathways starting at the raphe nuclei in the brain stem. Serotonin has been shown to have some involvement in complex processes, including mood, anxiety, sleep, circadian cycles, cognition, thermoregulation, sexual drive, and appetite.

Often in science, as we peel away the layers of the knowledge onion, we simply discover new layers. During the 1930s and ’40s, the serotonin story began by simply identifying the molecule and discovering a few of its simple properties—increasing intestinal motility/secretions and being released by platelets trying to stop a bleed by helping out with vasovasodilation. The next step was to figure out how serotonin fits into these physiologies, and good basic science discovered the serotonin transport pump on the surface membrane of the platelets and a serotonin receptor in the gastrointestinal tract.

Over the next 4 decades, the receptor part of serotonin’s story exploded, ultimately discovering 7 different families of serotonin receptors, with many families having subfamilies, allowing for heterogeneity of function. The 5HT-7 family was discovered in 1993, and the full sequencing of the human genome in 2003 increased our confidence that we had a basic understanding of the divergent serotonin receptors.

Intensive pharmaceutical research has developed serotonergic receptor-specific drugs with mechanisms of action that fit with what we currently know about this complex system. From the Editor
depressive episodes. In 1952, at Sea View Hospital on Staten Island, New York, Hoffman-LaRoche were studying 2 novel antituberculosis drugs—isoniazid and iproniazid—to treat infected patients. In addition to effectively treating the tuberculosis, the physicians observed significant improvements in the patients’ mood, appetite, and sense of well-being. Iproniazid was subsequently shown to be a potent inhibitor of the enzyme monoamine oxidase, which results in increased levels of serotonin, norepinephrine, and dopamine in the pre-synaptic neurons, and was approved by the US Food and Drug Administration (FDA) as the first antidepressant in 1958. In 1959, imipramine, derived from an antihistamine, was the second FDA-approved antidepressant. Imipramine, along with other properties, inhibits the presynaptic transport pumps in neurons that recycle serotonin and norepinephrine from synapses back into the pre-synaptic neuron, resulting in a global increase of these neurotransmitters in their corresponding synapses. Although through different mechanisms, iproniazid and imipramine shared the properties of increasing brain levels of both serotonin and norepinephrine (and dopamine with iproniazid).

Not coincidently, most of the antidepressant drug development research that followed in subsequent decades resulted in an armamentarium of drugs that by different mechanisms altered some part of the complex pathways of serotonin, norepinephrine, or dopamine. However, throughout these decades, research tirelessly pursued other potential drug candidates as well, realizing that depression is a complex syndrome with countless synergizing factors, including all dimensions of the biopsychosocial elements of human life.

Table 3 is a partial list of the wide range of treatments that have been shown to improve depression, either alone or in various combinations. In the field of psychopharmacology, current research has focused on the role of the glutamate system in contributing to this complex puzzle. Synaptogenesis and neuroplasticity—2 properties critical to brain health, adaptation, and learning—can be enhanced by most of the items listed in Table 3, and by much more. (Table 3 is available online.)

Through clinical observations, drugs that specifically blocked serotonin transport pumps showed a signal that in some cases this mechanism could improve anxiety. The FDA approved clomipramine in 1969 as the first drug for the treatment of obsessive-compulsive disorder (OCD). Clomipramine was synthesized by adding a chlorine atom to imipramine, which had the effect of increasing the binding at the serotonin transport pump relative to the norepinephrine transport pump in comparison to the other tricyclic antidepressants. The only other drugs that are FDA approved for OCD are the selective serotonin reuptake inhibitors (SSRIs) fluoxetine, sertraline, paroxetine, and fluvoxamine.

Significantly, the most effective treatment for OCD is a cognitive behavioral treatment called exposure/response prevention. However, early in treatment, or for patients who are not interested in psychotherapy to improve their OCD symptoms, SSRIs remain the first-line medications. SSRIs have also demonstrated efficacy for other anxiety disorders including panic disorder, social anxiety disorder, and posttraumatic stress disorder, with at least 1 SSRI having FDA approval for these anxiety disorders. However, psychotherapy ideally should also be part of the treatment plan.

Not surprisingly, despite the initial excitement in psychiatry during the SSRI explosion in the 1990s, it became clear that raising synaptic serotonin levels could only help some of our patients some of the time, and with a wide range of symptom improvement. Pharmacologically, the SSRIs are blocking all serotonin transport pumps (AKA re-uptake pumps) throughout the entire human body, resulting in ubiquitous elevation of serotonin levels everywhere. With the serotonin transport pump being a simple and basic component of the complex serotonin system, increased serotonin levels result in agonism of all 7 families (as well as the many subfamilies) of serotonin receptors.

Our understanding of the impact of this is rudimentary and mostly derived by patient-reported effects. Many of the common adverse events from SSRIs are likely due to the collateral effects on serotonin receptors, in which increased agonism would ideally be avoided. Additionally, blocking the serotonin transport pumps on platelets depletes platelet serotonin, decreasing the platelets’ ability to use serotonin for vasoconstriction at a bleed, hence increasing the body’s bleeding time—a well-established result of SSRI use. To come full circle with the discovery of serotonin, SSRIs result in agonism of the 5HT-3 and 5HT-4 receptors, increasing the adverse events of nausea/vomiting and gastrointestinal cramping/diarrhea, respectively, and decreasing the vasoconstriction component of how platelets stop a bleed.

In addition to the serotonin transport pump and the numerous and diverse serotonin receptors, there are many other targets that have been studied in an attempt to develop drugs to treat various psychiatric disorders targeting the serotonin system. These include precursors and enzymes involved in serotonin’s metabolic pathway, storage in presynaptic vesicles, and metabolic breakdown. Without a doubt, science, medicine, and psychiatry have learned a great deal about the serotonin system since its discovery in 1953. (A gross simplification of 2 serotonin neurons with a synapse between them is available online.)

Despite all that we know, the serotonin system in the brain remains a mystery. For that matter, the etiology to most disorders of the brain in psychiatry and neurology await continued discoveries. However, it really should be no surprise. In my medical school training in the 1980s, we called the brain a black box. We were taught that the brain is fully wired at birth. We did not believe

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**Table 1. Mechanisms of Action of Serotonergic Receptor-Specific Drugs**

<table>
<thead>
<tr>
<th>5HT receptor</th>
<th>Agonist/antagonist</th>
<th>Drug</th>
<th>Actual or putative clinical effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHT-1A</td>
<td>Agonist</td>
<td>Buspirone</td>
<td>Antianxiety, Antidepressant, Cognitive improvement</td>
</tr>
<tr>
<td>SHT-1B</td>
<td>Agonist</td>
<td>Triptans</td>
<td>Antidepressant, Antimigraine</td>
</tr>
<tr>
<td>SHT-1D</td>
<td>Agonist</td>
<td>Triptans</td>
<td>Antidepressant, Antimigraine</td>
</tr>
<tr>
<td>SHT-1E</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>SHT-1F</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>SHT-2A</td>
<td>Agonist</td>
<td>Palocarb/LSD, mescaline, Nefazodone</td>
<td>Antagonist, Antipsychotics, Halucinogen, Antidepressant, Decreases EPS</td>
</tr>
<tr>
<td>SHT-2B</td>
<td>Agonist</td>
<td>Fenfluramine</td>
<td>Psychosis, Causes cardiac valve fibrosis</td>
</tr>
<tr>
<td>SHT-2C</td>
<td>Agonist</td>
<td>mCPP</td>
<td>Antagonist, Agomelatine, Atypical antidepressants, Antidepressant, Anxiety disorder, Antipsychotics</td>
</tr>
<tr>
<td>SHT-3</td>
<td>Antagonist</td>
<td>Ondansetron</td>
<td>Antidepressant, Antimigraine</td>
</tr>
<tr>
<td>SHT-4</td>
<td>Agonist</td>
<td>Tegaserod</td>
<td>Increased bowel motility and secretions</td>
</tr>
<tr>
<td>SHT-5</td>
<td>Antagonist</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>SHT-6</td>
<td>Antagonist</td>
<td>—</td>
<td>Antidepressant, Procognition</td>
</tr>
<tr>
<td>SHT-7</td>
<td>Antagonist</td>
<td>Lurasidone, amisulpride</td>
<td>Antidepressant, Procognition</td>
</tr>
</tbody>
</table>
neuronal stem cells existed. Neuroplasticity and synaptogenesis were not yet part of our basic curriculum. Epigenetic, and even genetic, contributors were shrouded in darkness. The biopsychosocial model of psychiatric disorders was well established, but still in its infancy. All in all, it seems to me we are right where we should be: We know a little bit, but we do not know a lot.

The human brain has 80 billion neurons on average. Each neuron has a synaptic connection to roughly 10,000 other neurons. Hence, our brains have roughly 800 trillion synaptic connections. Wrap your brain around that number. It would be naïve to believe that targeting a single neurotransmitter, receptor, or circuit in the brain will cure any psychiatric or neurological disorder. However, we would be remiss if we did not try.

Over the years, decades, and ultimately centuries, our mission is to continue to expand our knowledge of the brain and utilize the tools that we do have at any point in time. As with all good medicine, we will continue to weigh and discuss the risks and benefits with each of our patients, allowing them to make informed decisions as to their preferred treatment plans.

The future of psychiatry is exciting. I am awed by the biography of serotonin that has been written since its discovery in 1935. Yet serotonin is but one letter in the encyclopedia of how the brain works—making a presence on page 1, but humbled by all that is still to be discovered.

References
As senior academic psychiatrists and psychopharmacologists, we reacted with similar puzzlement to a recent umbrella review and follow-up article by researchers in the United Kingdom.1,2 The review, by Moncrieff et al and published in Molecular Psychiatry (henceforth, “the review”), argued that there is “no support for the hypothesis that depression is caused by lowered serotonin activity or concentrations” and that “the serotonin theory of depression is not empirically substantiated.”

Two of the review authors published a follow-up article, “Depression is probably not caused by a chemical imbalance in the brain – new study.”2 This article’s data went well beyond those of the original review, claiming (inaccurately, in our view) that “antidepressants appear to have a generalized emotion-numbing effect”; that it is “impossible to say that taking selective serotonin reuptake inhibitor [SSRI] antidepressants is worthwhile”; and that “it is not clear that SSRIs do more good than harm.”

We suspect that the review authors sincerely believed they were publishing something extraordinarily newsworthy or controversial. The credulous popular media certainly thought so, and, predictably, antipsychiatry groups were quick to pounce on the UK group’s findings. Headlines all over the internet trumpeted variations of “Study says depression not caused by chemical imbalance, raising questions about antidepressants.”3 Media coverage of the review quickly morphed from discussion of serotonin into doubts about the value, efficacy, and safety of antidepressants, with many in the general public voicing alarm or heaping scorn on psychiatry,4 with a few notable exceptions.5

Such public consternation was completely understandable. In our view, the credulous, media-driven narrative generated by the review and the follow-up article amounts to well-worn rhetoric—and the review itself is little more than old wine in new bottles. Furthermore, we find at least 7 serious problems with the review’s claims (Table 1), each of which undermine the review’s thesis, as we will elaborate.

**TABLE 1. 7 Ways the Review and Its Conclusions Are Amiss**

1. There has never been a causally based “chemical imbalance theory” or a “serotonin theory” of depression espoused by academic psychiatrists, psychopharmacologists, standard psychiatric textbooks, or professional psychiatric organizations, at least in the United States.

2. Psychiatrists have known for decades that the etiology of depression and other mood disorders is extremely complicated and cannot be explained solely in terms of 1 or 2 neurotransmitters.

3. The review sampled a very small portion of a much larger universe of serotonin-related hypotheses and their applicability to psychiatric disorders and their treatment.

4. The report’s findings were not news, in that at least 4 previous reviews of the serotonin (5-HT) hypothesis (1954-2017) found that the total evidence was inconclusive or inconsistent.

5. The brain contains dozens of neurotransmitters, and hypotheses regarding the etiology of depression have extended far beyond serotonin—indeed, far beyond biogenic amines—to many other potential biological causes and risk factors. In some cases, layered models integrating several hypotheses have been developed.

6. Many effective drugs used in general medicine, neurology, and oncology act through unknown or multiple mechanisms; this fact is not an indictment of the drugs or those who prescribe them.

7. The precise mechanism of action of SSRIs is irrelevant to the safety and efficacy of these agents in the treatment of major depressive disorder. Although there is legitimate debate over the efficacy of long-term antidepressant use, the review contributes no new information in that regard.

Despite claims to the contrary,4 there has never been a full-blown theory of depression proposed by a monolithic entity called “psychiatry,” asserting that depression is directly caused by abnormal levels of 1 or more neurotransmitters.14 In fact, numerous statements from psychiatrists and researchers dating back to the 1960s include reasoning on why this is not likely. For example, pioneering psychiatrist Joseph J. Schildkraut, MD, and neuroscientist Seymour S. Kety, MD, explained this idea in 1967.”
Indeed, a detailed review by one of us (GD) found no references to a “chemical imbalance theory” of mental illness in any standard psychopharmacology textbook or peer-reviewed psychopharmacology literature over the past 30 years. The conflation of monoaminergic, catecholaminergic, or indoleaminergic hypotheses of depression with a so-called chemical imbalance theory of mood disorders is inaccurate.

Psychiatrists have known for decades that the etiology of depression and other mood disorders cannot be explained solely in terms of a single neurotransmitter—whether serotonin, norepinephrine, or some other biogenic amine. For more than 40 years, the operative paradigm in academic psychiatry has been the biopsychosocial model—which was articulated in rudimentary form by Schildkraut and Kety themselves, in the very passage quoted previously. Furthermore, in the period of 1990 to 2010, psychiatrists and neuroscientists proposed at least 17 other hypotheses regarding depression, with 8 additional ideas since then.11

The complexity of serotonergic systems and signaling in the brain is not captured in the review. Other detailed recent reviews suggest that the early serotonin studies did not capture the complexity of the 5-HT system and should be viewed as merely preliminary sampling of a very small part of the universe of serotonin-related hypotheses. Recent work in this area reveals that although serotonin systems are now much better characterized, additional work needs to be done.12 The review’s claim that psychiatric research on serotonin has yielded no useful information—and that this whole area of research should be brought to a close—does not accurately reflect the current scientific research program. On the contrary, more recent integrated theories—those that incorporate the significance of 5-HT systems with other depression hypotheses—are under active development. Several research groups are using multomics approaches, in which the data sets are multiple omics, such as the genome, the proteome, and the transcriptome.

Approaches that examine serotonin and its metabolites have been used by some research groups to predict antidepressant response and have been internally replicated.13 A recent review of 50 studies of the metabolomics of major depression concluded that several metabolites are altered in major depression, including kynurenine—a tryptophan metabolite thought to be a key mediator of psychiatric illness that interfaces with the immune and mood systems.14

Information in the review was hardly news to psychiatrists. As shown in Table 2,15-17 at least 4 investigations of the 5-HT hypothesis found inconclusive or inconsistent evidence. The most recent review (2017) concluded that additional evidence was needed to support the model and resolve inconsistencies. These authors also proposed several new 5-HT receptor-based hypotheses.11

The brain contains about 50 to 100 neurotransmitters.15 Hypotheses regarding depression have extended far beyond serotonin—in fact, far beyond biogenic amines. The review is focused narrowly on serotonin and does not address other small molecule or neuropeptide neurotransmitters that may figure in antidepressant action. Furthermore, the review does not address effective nonserotonergic antidepressants like bupropion16 or antidepressants like vortioxetine, which have very complex serotonergic effects.17

In the area of drug development, there has been active debate about whether a specific mechanism of action and/or drug target is necessary for a medication to be approved. Many medications like aspirin, acetaminophen, and digoxin were used for decades before a putative mechanism was identified. One of us (GD) recently reviewed the package inserts of drugs that were FDA approved as disease-modifying drugs for multiple sclerosis.18 Eighteen drugs have been approved since 1993, yet the mechanism of action for 17 of the 18 medications is listed as unknown.

The trade-offs of searching for a mechanism of action or drug target—as opposed to phenotypic screening for drug effects—have been discussed by Davis, who points out that disease complexity is important in considering mechanism of action and drug target identification, especially in complex central nervous system diseases.19 In any case, the precise mechanism of action of SSRIs cannot be determined from the data in the review.

The techniques described in the review were not designed to determine antidepressant efficacy, which is determined by randomized controlled clinical trials. Thus, no conclusions can be drawn from the review regarding antidepressant efficacy, or the “good versus harm” associated with antidepressant treatment. Although the topic is beyond the scope of this commentary, there is convincing evidence that

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**TABLE 2. Selected Reviews of the Serotonin Hypothesis in Depression**

<table>
<thead>
<tr>
<th>Year</th>
<th>Hypothesis</th>
<th>Authors</th>
<th>Methods and conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1954</td>
<td>Serotonin hypothesis of mental diseases</td>
<td>Woolley and Shaw</td>
<td>Effect estimated from pharmacological probes (LSD and isomers), effects of antidepressant medications (monoamine oxidase inhibitors and tricyclic antidepressants), and estimated 5-HT content of tissue and fluids in animal experiments. Conclusion: Inconclusive</td>
</tr>
<tr>
<td>1967</td>
<td>Serotonin</td>
<td>Schildkraut and Kety</td>
<td>Catecholamine hypothesis of affective disorders, experimental findings for histochemical fluorescence, and pharmacological probe studies were discussed in detail. Changes in the metabolism of biogenic amines were seen as unlikely to account for the “complex phenomena of normal or pathological affect.” Conclusion: Inconclusive—confirmation requires direct demonstration in naturally occurring illness</td>
</tr>
<tr>
<td>1978</td>
<td>Serotonin revisited</td>
<td>Murphy, Campbell, and Costa</td>
<td>DETAiled review looking at modern findings in 5-HT research. Very positive findings in some areas of research (reduced CSF HIAA levels in depression). Conclusion: Inconclusive, but further study definitely indicated</td>
</tr>
<tr>
<td>2017</td>
<td>Serotonin revisited</td>
<td>Carhart-Harris and Nutt</td>
<td>Proposed biartite model of 5-HT mediated by predominant receptors 5-HT$<em>{1A}$ (passive coping/stress relief) and 5-HT$</em>{2A}$ (active coping/plasticity). Extensive narrative review, but discussion of 5-HT receptors was restricted due to system complexity. Reviews the effects of pharmacological probes (LSD, MDMA, psilocybin), PET imaging, and clinical/preclinical behavioral pharmacology of selected receptors. Conclusion: Additional evidence needed from future research. Authors proposed an entirely new set of 5-HT receptor-based hypotheses that seek to answer: “What is the function of brain serotonin?”</td>
</tr>
</tbody>
</table>
We believe that antidepressant treatment should be undertaken conservatively, monitored closely, and regarded as only a single component of a comprehensive, biopsychosocial approach to depression, generally including talk therapy.

most antidepressants are safe and at least moderately effective in the acute treatment of moderate to severe major depressive episodes.24-26

Clinical Approach to Depression

As several neuroscientists and researchers pointed out in response to the review, the role of serotonin in mood disorders is by no means settled science, and there may well be some role for this neurotransmitter in some types of depression, which is almost certainly a heterogeneous group of disorders.27 That heterogeneity complicates efforts to identify consistent biomarkers of psychiatric illnesses, including major depressive disorder. Although there have been some critiques of the review, psychiatrist and researcher Michael Bloomfield, MD, states the issues particularly well:28

I don’t think I’ve met any serious scientists or psychiatrists who think that all [cases] of depression are caused by a simple chemical imbalance in serotonin. What remains possible is that for some people with certain types of depression... changes in the serotonin system may be contributing to their symptoms. The problem with the review [by Moncrieff et al] is that it has lumped together depression as if it is a single disorder, which from a biological perspective does not make any sense.

Most importantly, the review does not in any way impugn the overall safety and effectiveness of serotonergic antidepressants in the acute treatment of moderate-to-severe major depression. That said, we believe that antidepressant treatment should be undertaken conservatively, monitored closely, and regarded as only a single component of a comprehensive, biopsychosocial approach to depression, generally including talk therapy. As such, patients should be educated regarding all 3 components of mood disorders: biological, psychological, and sociocultural.

Compared with treatment of an acute major depressive episode, long-term use of antidepressants (eg, over several years) presents a more complicated picture with a thinner evidence base, and this merits a careful risk/benefit discussion with patients.35 Similarly, particular care must be taken in discontinuing long-term antidepressant use.29 Finally, the risk/benefit discussion concerning antidepressants (and other biological treatments in psychiatry) should be approached in the same way as the physician would approach any other serious medical intervention.

Concluding Thoughts

Depression is a complex, heterogeneous disorder with biological, psychological, and sociocultural determinants and risk factors. Very few—if any—US psychopharmacologists and academic psychiatrists have ever endorsed a sweeping chemical imbalance theory of mood disorders. Historically, psychiatrists have never explained clinical depression solely in terms of reduced serotonin or any specific neurotransmitter. Many drugs in clinical medicine work through unknown or multiple mechanisms, as SSRIs do, and this does not affect their safety, efficacy, or approval for medical use. Results of placebo-controlled studies often provide evidence that serotonergic antidepressants are safe and effective in the treatment of acute major depressive episodes. If serotonergic agents are not helpful, antidepressants from other classes (eg, noradrenergic/dopaminergic agents) may be considered. Finally—and perhaps most importantly—we hope that patients and clinicians are not deterred from the use of antidepressants by the review, or by the fact that SSRIs’ mechanism of action is complex and not completely understood.

ACKNOWLEDGMENTS: The authors thank John J. Miller, MD, Heidi Anne Duer, MPH, and Cynthia M.A. Geppert, MD, MA, MPH, for encouraging this contribution.

References
Contingency Management Is a Powerful Clinical Tool for Treating Substance Use
Research Evidence and New Practice Guidelines for Use

Sterling M. McPherson, PhD; Sara Parent, ND; André Miguel, PhD; Michael McDonell, PhD; John M. Roll, PhD

Contingency management (CM) is an effective behavior change technique commonly used to treat substance use disorders (SUDs). CM is one of the most effective behavioral interventions for initiating and maintaining abstinence from most types of commonly used drugs and alcohol.

Background and Rationale
CM-based treatments for SUD originate in basic behavioral science, namely the operant conditioning literature. Operant conditioning is a type of learning in which behavior is modified or maintained through the consequences it produces. In the context of SUD treatment, CM typically modifies substance use by delivering tangible, positive reinforcers (e.g., prizes, vouchers, or monetary reinforcement) in exchange for evidence of the performance of the targeted behavior, such as the submission of a drug-negative urine sample.1

Several meta-analyses have found CM to be among the most effective interventions for SUDs, in addition to being effective at promoting treatment retention and medication adherence.2,3 Moreover, clinical trials have consistently shown that CM is also a cost-effective technique.4,5 Indeed, studies conducted over the past 30 years have found that CM can be used to promote abstinence from substances including cocaine,6 methamphetamine,7 tobacco,8 alcohol,9 opioid,10 cannabis,11 and benzodiazepines.12 Further, the aforementioned meta-analyses have also found CM to be effective among highly diverse populations, including pregnant women, adolescents, veterans of war, individuals with serious mental illness, unhoused individuals, those from racial and ethnic minority backgrounds, LGBTQ+ community members, and individuals with HIV and hepatitis. Notably, CM’s consistent effects during treatment across diverse trials may be indicative of CM’s ability to improve long-term treatment outcomes, in light of evidence indicating that longer abstinence during treatment is associated with better long-term treatment outcomes.16,17

Optimizing Therapeutic Effects
Research results suggest that CM must have 3 key ingredients to optimize utility (Table). The first is the frequency with which the reinforcer is delivered. Studies suggest that reinforcers should be provided at least twice weekly to enhance the efficacy of CM for SUD management.18 The second ingredient is the immediacy of the reinforcer, or the exchange delay (i.e., the shorter the period between the performance of the targeted behavior and delivery of the reinforcer, the greater likelihood of behavioral change).19 The third ingredient is the magnitude of the reinforcer. Although higher-magnitude reinforcers increase the chances of behavior change, they also increase the cost of the CM intervention.20 In at least 1 study, however, it is notable that the average reinforcer actually costs around 40% of the maximum amount.21

Implementation Challenges
FUNDING
Although more than 30 years of research evidence collected throughout the world supports the effectiveness of CM, wide-scale implementation of CM in clinical care has been limited, particularly due to funding and regulatory issues. While reinforcers are commonly used in health care to increase a targeted behavior (e.g., gift cards for completing a health assessment), the recommended frequency (twice weekly) and magnitude of CM reinforcers is unique. Historically, funding for CM programs has relied on grants, donations, and funding from federal sources. Currently, the Substance Use and Mental Health Services Administration (SAMHSA) allows grantees to spend up to $75 per patient for...
Previously skeptical clinicians noticed that CM had not only improved response to treatment, but also helped improve therapeutic alliances with patients and increased practitioners’ job satisfaction.

CM incentives, although there is limited evidence for the efficacy of this amount.

In addition to funding, the prohibition against the use of reinforcers with Medicaid and Medicare patients through antikickback regulations, has produced a regulatory roadblock. Until recently, it was unclear if CM violated these prohibitions; however, in 2019, the Office of the Inspector General published a document providing guidance on how CM can be used within specific parameters. This has led to increased interest in CM, with state-level implementation underway in Montana, Washington, and California. California received a Medicaid demonstration waiver for the state’s CM pilot, planned to cost more than $50 million, that will include as many as 200 sites. Importantly, these implementations of CM include models that are based on research evidence with funding for reinforcers varying from $325 to $599. These policy changes are also important elements to ensure the success of a CM program.

**TABLE. Keys to Optimize Contingency Management Utility**

<table>
<thead>
<tr>
<th>Frequency of reinforcer</th>
<th>Twice weekly</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 Immediacy of reinforcer</td>
<td>The shorter the delay, the greater the likelihood of behavioral change</td>
</tr>
<tr>
<td>3 Magnitude of reinforcer</td>
<td>The higher the magnitude, the greater the likelihood of behavioral change</td>
</tr>
</tbody>
</table>

**PHILOSOPHICAL AND MORAL CONCERNS**

One important challenge for CM implementation includes philosophical and/or moral concerns about “paying substance users” to stop using drugs; another is the belief that the effect may not persist after CM is concluded. Implementations of CM can represent a paradigm shift for many systems and clinicians who have been required to deliver punitive consequences when substance use occurs. When objective evidence of use is recorded, clinicians focus on strengths-based feedback, such as praise for attendance, and encouragement that the next opportunity for reinforcer will occur again in just a few days. They can further engage the patient by discussing what reinforcer they are excited to work toward, what reinforcer they are excited to work toward, and encouragement that the next opportunity for reinforcer will occur again in just a few days.

Although evidence indicates that CM is associated with increased attendance, use of reinforcers to increase revenue from billable encounters is prohibited and should be avoided.

Another tip includes using an electronic CM platform system to calculate and monitor reinforcer magnitude and distribution. CM often incorporates a reinforcement schedule that includes escalating reinforcement magnitude as increased durations of abstinence are achieved, as well as loss and recovery of the escalation bonus if and when a return to use and a return to sustained abstinence occur (known as “reset” and “recovery”). Although adding these features to a CM program increases the complexity, the therapeutic benefit is well documented and can be executed consistently by using an electronic CM platform. Notably, in various stages of development are a number of phone apps (with accompanying web-based management portals) that could help clinicians, staff, and patients deliver and receive reinforcers more readily; such a system would reduce staff burden for tracking and calculating reinforcer values.

Lastly, CM can represent a paradigm shift for many systems and clinicians who have been required to deliver punitive consequences when substance use occurs. When objective evidence of use is recorded, clinicians focus on strengths-based feedback, such as praise for attendance, and encouragement that the next opportunity for reinforcer will occur again in just a few days. They can further engage the patient by discussing what reinforcer they are excited to work toward, orienting the patient toward the reinforcement inherent in CM.

Obtaining initial training and ongoing technical support from CM experts is key to successful implementation and compliance with Office of Inspector General regulations. Several teams have developed extensive training materials that provide best-practice guidance on CM implementation, including didactic trainings, ongoing coaching, and technical support. Driven by the escalating prevalence of methamphetamine use and recent changes in federal policy, the rapid dissemination of CM can bring this feasible, strength-based approach to millions of people affected by stimulant use disorders throughout...
the United States—if the unique challenges that
the method presents can be overcome.

Concluding Thoughts
One of the biggest barriers to effectively utilizing
CM in real-world treatment situations has been
the lack of adequate public policies to finance
CM interventions. Convincing policy makers why
CM should be more broadly integrated into drug
and alcohol use disorder treatment has proven
difficult. Nonetheless, CM interventions are being
applied in a variety of clinical practices through-
out the United States and the United Kingdom.27
For example, CM is being increasingly used as
the USD treatment of choice within the Veterans
Administration system in the United States.28
Since 2011, the Veterans Administration has
successfully integrated CM into 70 of its intensi-
outpatient substance abuse treatment clinics
for veterans.29 At the same time, the National
Health Service in the United Kingdom has also
implemented CM into its USD treatment guide-
lines, and CM is currently being offered at several
treatment facilities.30

Investigations of CM dissemination are cur-
rently underway, including studies designed to
better understand systemic and clinician vari-
ables that impede or facilitate CM implementa-
tion.23,24 One of the most important pieces of
that has emerged in the CM literature,
especially in light of the political challenges, is
that CM is a cost-effective treatment option.6,7
This should lead to greater adoption across the
US health care system, which is in desperate
search of economically viable alternatives in the
face of scarce and diminishing resources.

A final crucial aspect of CM that makes it
amenable to several different adaptations and
optimizations is that CM produces virtu-
ally no adverse events and can be combined
with virtually any other form of treatment.30
This makes CM both effective and amenable
to ongoing experimentation and optimization efforts
cross a diverse array of settings and populations
that will only be leveraged further by ongoing technological, psychosocial, and
pharmacological developments.

Dr McPherson is director of the Program of Excellence
in Addictions Research; assistant dean, research; and
a professor at the Washington University School of Medicine.
He is also associate director of research for analytics and discovery at the
Providence Medical Research Center and head and
principal investigator of the Analytics and Psychophar-
macology Laboratory. Dr Parent is a scientific assistant at
WSU. Dr Miguez is an associate professor at WSU Elliott S. Floyd College of Medicine.
Dr McDonell is a professor in the Department of Community and Behav-

Oral造福和 Drug

References
Further Healing Thyself

H. Steven Moffic, MD
Special Report Chair

Last month in our Special Report, 2 papers discussed the wellness risks of physician substance abuse and the benefits of work-life balance. These are ethical ways to help our colleagues and ourselves.

As several more papers on the subject show in Part 2 of this Special Report, there are many places to touch upon and embrace the elephant of physician wellness.

Systems that disempower physicians and other health care professionals are the major cause of our burnout epidemic. That presents a major challenge: unless we are in a leadership position, there is not a lot each of us can do to improve the systems in which we work.

Yet, as these additional papers indicate, there is still quite a lot that each of us can do for our own wellness. So much so, that you will find additional articles online.

In one article, you will find 8 sound tips for preventing burnout. The last tip is simple but important: “remember your purpose.”

Remembering one’s purpose leads, in turn, to the article “The Alluring Mistress: Reflections From my Affair With Medicine.” Although personal psychotherapy was more or less required as a therapeutic vessel 50 years ago when I was in training, it is no longer expected. This personal article of reflections was an inspiring self-disclosure of how a psychiatrist, with help, realized what was really important in his life. This, in turn, led to a major change at work and much improved wellness. Some degree of this sort of soul-searching may be the lodestar for physician wellness, for it is what each of us can control the most.

Dr Moffic is an award-winning psychiatrist who has specialized in the cultural and ethical aspects of psychiatry. A prolific writer and speaker, he received the one-time designation of Hero of Public Psychiatry from the Assembly of the American Psychiatric Association in 2002. To create a better world, he is an advocate for treating mental health issues related to climate instability, burnout, Islamophobia, and anti-Semitism. He serves on the Editorial Board of Psychiatric Times™.
The Alluring Mistress
Reflections from My Affair With Medicine
Frank Clark, MD

**Mistress in disguise**

**Insight dismisses folly**

Joy summons true self

Society is fraught with infidelity. According to the American Association for Marriage and Family Therapy, national surveys indicate that 15% of married women and 25% of married men have had extramarital affairs. We are aware of the acute and chronic deleterious effects that these nefarious behaviors can have on the family unit. They include distrust, low self-esteem, depression, and anxiety. Often, affairs are in response to an individual’s attempt to fill a void in their relationship—to find something that they feel is missing. They ingest a concoction filled with enticing nutrients that provide the false promise of dopaminergic zeal. This promise quickly fades, leaving the soul once again parched and searching for its next lover.

We as physicians are not immune to this gravitational pull toward extramarital affairs. I can attest to this as someone who has been involved with my mistress throughout my career. She tempts you with long leadership titles in your signature line when sending emails. She whispers in your ear that ascending the social/professional ladder is the true meaning of success. She recognizes your moxie and suffocates you with unreeling opportunities. She masquerades as an angel in a white coat, but her looks are deceptive. Her name is Medicine.

**Never Slowing Down**

Throughout my life, family members, friends, and colleagues have posed the same question to me: “I would usually smile in response to their query to realize, was rooted in a core belief that my identity was about being a successful physician. Most days, I was exasperated, and on occasion, I would even cry in the shower before going into work. The bond between my daughter and me was fragile, and at times, my wife and I were like 2 ships sailing in the wind that could capsize at any given moment. I did not like the person I had become. I was a stranger in my own body that was is need of repentance and rejuvenation.

The providential moment of enlightenment descended upon me when I turned 40 years old. Transformation occurred with the aid of prayer, family support, and numerous sessions with my therapist. I became more aware of and in tune with my true identity. My faith in God has always guided me through the joys and storms of my life. I had to remind myself that my identity lies within. I realized that being a physician is just part of my identity puzzle. I am a father, husband, son, friend, visionary, creator, and poet.

It is refreshing to rediscover who one truly is in a world that offers the deceptive fruit of success. In October 2021, I advocated for myself and made the transition to a new clinical environment and out of a leadership role. My spirit has been at peace since the transition. I am present more than ever in my wife’s and daughter’s lives. I have had more time to focus on the pieces of my wellness puzzle that I neglected, such as writing poetry. I embrace the power of saying “no” and setting healthy boundaries. I have nothing to prove.

**Concluding Thoughts**

The journey of discovering the self requires a growth mindset and a willingness to admit that we are constantly evolving. My hope is that we all confront our mistresses of life that latch on to our unhealed wounds. The love affairs will persist and invade various areas of our life, until we finally face vulnerability in the mirror and embrace it.

Peace and blessings to you.

**Dr Clark** is an outpatient psychiatrist at Prisma Health-Upstate and clinical associate professor at the University of South Carolina School of Medicine. Greenville. He served on the American Psychiatric Association’s Task Force to Address Structural Racism Throughout Psychiatry, and he currently serves as the Diversity and Inclusion section editor and advisory board member for Psychiatric Times®.

**References**


8 Tips for Psychiatrists to Prevent Burnout

Doug Newton, MD, MPH

In 2018, the American Psychiatric Association found that burnout among psychiatrists was nearly 50%. This number may be even higher as we persist through a global endemic disease, social and political unrest, and increasing economic stressors. In many states, the collateral impact on health care will only be exacerbated by the recent Supreme Court decision to reverse Roe v Wade. This has led to increased burden on psychiatrists, our patients, and our colleagues in the medical field who turn to us for assistance.

It is important to note that the term burnout in itself can be polarizing and create stigma. It can place blame on the individual and does not take into account systemic or structural barriers that lead to untoward distress. At its core, burnout is an imbalance of empathy and self-compassion. So, what can we do to improve self-compassion and empathy as mental and behavioral health providers? My answer: We cannot forget to help ourselves before we can possibly help others. What follows are 8 tips.

1. Identify the problem. Though seemingly obvious, it is not. Cardinal signs of waning compassion and empathy include emotional exhaustion, depersonalization, and a decreased sense of personal accomplishment in work or in life. In the best interests of our patients, we need to identify it in ourselves and among our peers. There are self-assessments, including the Maslach Burnout Inventory, that can help.

2. Know you are not alone. We all are part of the human condition. Psychiatrists are not immune to what our patients and society are going through. Moreover, you are not the only psychiatrist or health professional suffering. Acknowledge it; do not stuff it down.

3. Stay connected. On personal and professional levels, there is a growing and persistent need to tackle loneliness and isolation among our family, friends, patients, and peers. The loneliness epidemic predates, but has been exacerbated by, the global COVID-19 pandemic. The surgeon general of the United States, Vivek Murthy, MD, MBA, has emphasized the importance of connection in our lives. Make time to reach out to colleagues, family, and friends.

4. Practice self-care. Although difficult in times of stress and overwhelming schedules, proper sleep, diet, and exercise are paramount. At the same time, be kind and do not place more stress and blame on yourself if you are unable to accomplish these tasks. Remember, starting small can make a big difference. Sometimes it can be as simple as taking a few minutes to garden, take a walk in nature, or commit to less screen time at night to get started in a positive direction.

5. Reduce or avoid substances of abuse. We know all too well the impact exogenous neurochemical depressants and stimulants can have on our patients. We are no exception. On the contrary, physicians are at heightened risk. If you or any of your colleagues need help, please seek it. There are anonymous resources through the Federation of State Physician Health Programs.

6. Prioritize teamwork. Studies have shown that being part of a treating team not only improves patient outcomes, but also fosters a sense of well-being for clinicians. If you are not part of a group practice or academic center, there are opportunities to collaborate and share knowledge. If you are in a remote, individual practice environment, companies like SonderMind can help facilitate virtual, supportive peer communities.

7. Stay curious. Continuously learn and grow not just in your professional field to better serve your patients, but also for yourself. Use self-inquiry, and question how certain situations or circumstances impact how we feel and react.

8. Remember your purpose. We are drawn to our profession to help others. We are mission-driven individuals, yet for many, psychiatry is not the only endeavor that gives us joy and purpose. Find creative or philanthropic outlets that fill your cup. Whether you want to call it altruism, religion, or spiritualism, studies have shown a sense of higher purpose promotes well-being.

Lastly, please remember, you are not the problem. However, through caring for yourself and staying connected to others, you can be the solution.

Dr Newton is the chief medical officer at SonderMind.

References
The text includes tables, proper nouns, and proper names. It details the metabolic changes associated with antipsychotic drugs, emphasizing hyperglycemia/diabetes mellitus, dyslipidemia, and weight gain. It also discusses the need for continuous treatment with these medications and the potential risks associated with their use. The text mentions the need for continued treatment and reassessment, stressing the importance of monitoring patients for adverse effects.
ABILIFY MAINTENA® (aripiprazole)

Potential for Cognitive and Motor Impairment: ABILIFY MAINTENA, like other antipsychotics, may impair judgment, thinking, or motor skills. These effects may lead to falls, especially among older adults. Falls may cause fractures or other injuries. Patients, their caregivers, and clinicians should be aware of this risk and monitor for these symptoms, especially during the initial treatment phase.

Other Adverse Reactions: Additional adverse effects that were not considered to have significant clinical implications, or 5) which occurred at a rate equal to or less than placebo.

Clinical Trials Experience:

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

- Increased Mortality in Elderly Patients with Dementia-Related Psychosis
- Neuroleptic Malignant Syndrome
- Metabolic Changes
- Nervous System Disorders: infrequent

Table 5: Clinically Important Drug Interactions with ABILIFY MAINTENA:

<table>
<thead>
<tr>
<th>Concomitant Drug</th>
<th>Clinical Rational</th>
<th>Clinical Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxetine, fluoxetine</td>
<td>Strong CYP3A4 inhibitor, e.g., strong CYP3A4 inhibitors increase the exposure of aripiprazole.</td>
<td>Use concomitant use of ABILIFY MAINTENA with caution in combination with CYP3A4 inhibitors.</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors</td>
<td>Strong CYP3A4 inhibitors</td>
<td>Use with caution.</td>
</tr>
</tbody>
</table>

DRUG INTERACTIONS: Drugs Having Clinically Important Interactions with ABILIFY MAINTENA

This table does not include adverse reactions that had an incidence equal to or less than placebo.
Extrapyramidal and/or withdrawal symptoms, Clinical Considerations:
Fetal/Neonatal Adverse Reactions:
Clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms. There are programs/pregnancyregistry. Consider the benefits and risks of ABILIFY MAINTENA and possible risks to the fetus when prescribing ABILIFY MAINTENA during pregnancy. For more information contact the National Pregnancy Registry for Atypical Pregnancy.

ABILIFY MAINTENA has not been studied in children 18 years of age or younger.

Pediatric Use: ABILIFY MAINTENA has not been studied in children 18 years of age or younger. The safety and effectiveness of ABILIFY MAINTENA have not been established in children.

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Common adverse reactions (reported in at least 5% of all overdose cases) include vomiting, somnolence, and tremor. Other clinically important signs and symptoms observed in one or more patients with aripiprazole overdosage (alone or in combination with other substances) include acidosis, aggression, aspartate aminotransferase increased, atrial fibrillation, bradycardia, coma, confusional state, convulsion, blood creatine phosphokinase increased, depressed level of consciousness, hypertension, hypokalemia, hypotension, increased, blood creatine phosphokinase increased, depression, delirium, dizziness, drowsiness, dysphoria, fever, headache, loss of consciousness, GCS complex prolonged, GCS prolonged, pneumonia aspiration, respiratory arrest, status epilepticus, and tachycardia.

Management of Overdosage: In case of overdose, call the Poison Control Center immediately at 1-800-222-1222.

To report SUSPECTED ADVERSE REACTIONS, contact Otsuka America Pharmaceutical, Inc. at 1-800-222-1222 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

For more information, visit www.abilifymaintena.com. or call 1-800-441-6763.

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Acculturative Stress: How to Help Immigrant Students

Karen Quan, MS4; Kimberly Ho Misiaszek, PhD; Flavia DeSouza, MD

Immigrant-origin students are increasingly becoming the face of US higher education. As such, mental health professionals must understand the acculturation process, as well as the relationship between acculturative stress and well-being of young adults, to more effectively address the ongoing mental health crisis in students.

CASE EXAMPLE “Christine” is an 18-year-old woman in her first year of college. At 14, she immigrated from South Korea to the United States with her parents, who moved to pursue their doctoral degrees. Christine performed well in her international high school and was accepted into a prestigious, predominantly white college on an academic scholarship while her parents wrapped up their programs and returned to South Korea. However, during her first college semester, Christine had trouble maintaining the high grades that seemed to come naturally to her in high school. She could not seem to manage her time and was often late for or missed classes. When she was in class, she had difficulty following the instructors. She joined the Korean American Student Association, a small student club, seeking out advice on how she could better manage in her first year of college. However, she had difficulty connecting with her US-born peers, as she felt “too Korean.” She missed her family and the ease of connection she had with her peers back home. By her second semester, in the context of both the pandemic isolation and aggression toward people of Asian descent, Christine lost the drive to attend her classes and subsequently began failing a course. Feeling disappointed with herself and too ashamed to speak with her parents, she sought help at her college’s student mental health center after being recommended to do so by her dean.

What Is Acculturative Stress?
A nationwide survey showed a rapid deterioration of mental health among the college student population during the COVID-19 pandemic, worsening the preexisting college student mental health crisis. Colleges have been struggling to meet the increasing demand for student counseling and mental health services. US college counseling centers are insufficiently staffed and underfunded, and often operate on waitlists. Further, college mental health centers are often not equipped to work with immigrant and international students, as opportunities for cultural responsiveness training in professional psychology are scarce within both doctoral training programs and professional development contexts.

Acculturative stress refers to the specific stress reaction of immigrants in response to their acculturation process, which can be described as the “changes following contact between culturally different people.” Alternative to culture shock, a term with negative connotations that implies involvement of a singular culture, acculturative stress is a preferred term to describe the phenomenon that affects performance, mental and physical health, and sociocultural adjustment. Stressors can be social, cultural, familial, environmental, institutional, or perceived difficulties (Figure).

Acculturative stress can lead to anxiety, depression, somatization, and behavior problems, as well as exacerbate underlying psychiatric disorders. Thus, recognizing acculturative stress may be an integral aspect in an immigrant student’s mental health care to consider in their psychiatric evaluation. In Christine’s case, going to college led to the loss of the social support of family, friends, and community that may have provided the scaffolding to buffer acculturative stress.

How to Provide Support for Stress-Buffering
Students need to feel that they have adequate support to handle the stress around them. Stress arises when individuals believe they do not have the tools or coping response to handle a demanding or threatening situation. Although stress and stressful situations are parts of life, managing stress in a healthy, productive way does not always come naturally. Identifying and reinforcing buffers can help mitigate the pathogenic effects of stress. More simply put, keeping the stress...
TABLE. Riverside Acculturative Stress Inventory

<table>
<thead>
<tr>
<th>Factor</th>
<th>Work challenges in school</th>
<th>Language skills</th>
<th>Intercultural relations</th>
<th>Discrimination</th>
<th>Cultural isolation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Does your background make you feel like you need to work harder compared to your peers who are not immigrants?</td>
<td>How do your language skills affect your performance and being understood by others?</td>
<td>What are your feelings about your accent?</td>
<td>Have you faced any discrimination in the classroom or from peers?</td>
<td>Are there others who share the same culture as you? Do you find your environment culturally rich?</td>
</tr>
</tbody>
</table>

1 USE AN ACCULTURATIVE STRESS SCALE

A variety of scales are available, including the Acculturative Stress Scale for Chinese College Students scale (ASSCS); the Social, Attitudinal, Familial, and Environmental scale (SAFE); the Race-Based Traumatic Stress Symptom Scale; and the Riverside Acculturative Stress Inventory. They all address similar situations. By reinforcing to students that they lessen the perceived potential harm of stressful resources—could buffer the stress response and help better support students as they grapple with stressors. We provide 4 strategies that mental health counselors and clinicians can adopt to help better support students as they grapple with differences in their culture of origin and their new majority culture.

2 PROVIDE LANGUAGE TOOLS TO COMBAT SOCIAL CONSTRAINTS

While feelings of belonging and support are integral for stress buffering, social constraints interfere with the cognitive and emotional processing of stress. Social constraint refers to an individual’s perception that their social networks are unsupportive or un receptive to discussions regarding stress related to their cultural background. Racial and ethnic minorities who have higher social constraints may experience more psychological distress. In a study on acculturative stress in Hispanic/Latino and Asian immigrant college students, Asians who felt constrained by their social network to not express their thoughts and feelings about their acculturative stress experienced more psychological distress. It is important to recognize that it is not necessarily a lack of support that attributes to acculturative stress, but rather a mismatch between desired and received support. Counselors can offer interventions to reduce stress caused by social constraints, such as exercises with students to identify their social constraints and to develop the language to effectively communicate their thoughts, feelings, and needs. Developing alternative outlets for emotional expression, such as expressive writing or online support groups, can give students ownership of their experiences and their voices, which can be helpful in situations where support from their community cannot be attained.

3 ENCOURAGE SELF-AGENCY

Mental health professionals should encourage students to explore self-agency and develop values that can support them making their own decisions while also preserving their cultural heritage. Those who adopt values of individualism and self-agency are more likely to have positive attitudes toward seeking professional psychological help, which is important for immigrant students who struggle with mental health disorders. If these skills of self-agency conflict with the student’s cultural or ethnic identity and values, it is vital for clinicians to help students integrate and reconcile those incompatibilities and hopefully maintain their bicultural or multicultural identity. Taking pride in both cultural backgrounds seems to be associated with well-being for first-generation and second-generation immigrants. The discarding of one’s heritage culture, rather than adapting to the United States, is associated with increased health risk behaviors. Strong racial identification and racial pride can also provide a buffer against discrimination and distress and are connected to positive mental and physical health outcomes.

4 PRACTICE WITH HUMILITY AND CURIOSITY

Most clinicians who work at academic mental health centers are not immigrants and do not have extensive experience working with or treating immigrant students. Therefore, practicing cultural responsiveness, such as keeping an open mind and learning more about different cultures without overgeneralizing, will help providers better serve this population. In the United States, race and ethnicity are often conflated, resulting in racialization—the process of stereotyping a group of peoples—of immigrants who may not fit into their “assigned” racial role. For instance, the racial group Black consists of many ethnic groups including but not limited to African Americans, Afro-Caribbean immigrants, and African immigrants, meaning that those classified as Black may not all identify as African American. School-based and clinic-based interventions that work for one group may not apply to another. With this in mind, we must approach each student’s case based on their individual story and context.

Concluding Thoughts

For Christine, an essential part of her care involved connecting with a therapist who helped her navigate through the guilt she experienced for struggling academically in the face of her parents’ sacrifices and the shame of “not measuring up” to the expectations of her family. Because the Korean immigrant community she grew up in had many cultural values that differed from those of her Korean American peers, she had to reassess her own ethnic identity as a Korean in America, especially during a time of increased Asian hate. Her therapist also recognized that while the acculturative stress caused significant psychological distress, Christine still needed further care. History-taking by her psychiatrist revealed that Christine had symptoms of attention-deficit/hyperactivity disorder as a child. These symptoms were missed due to her parents’ heavy involvement in her education and were exacerbated by the increasing cognitive challenges and acculturative stress of her new environment. She was started on Ritalin, and with continued therapy, she saw improvement in her grades and increased ability to navigate her new environment.
generation immigrants continue to make up more of the higher-education population in the United States, mental health professionals must be equipped to help this growing population with their needs. The ability of mental health counselors and clinicians to recognize acculturative stress and to help provide support for immigrant college students becomes even more pertinent as the school year starts again. Hopefully, this year, we will be more ready.

Ms Quan is a fourth-year medical student at Georgetown University School of Medicine. Dr Misiaszek is a licensed clinical psychologist, clinical director, and assistant professor in the Department of Educational and Psychological Sciences at the University of Miami. Dr DeSouza is a child and adolescent psychiatry fellow at Medstar-Georgetown, board-certified adult psychiatrist with attending privileges at Howard University Hospital, and an American Psychiatric Association SAMHSA fellow.

References
Special Populations

COMMENTARY

Just the Tip of the Iceberg: Psychiatric Implications of Overturning Roe v Wade

Nada L. Stotland, MD, MPH

Author’s note: Throughout this commentary, I use female pronouns and terms to designate the individuals who have abortions. I am aware that there are individuals who identify as male, transgender, or nonbinary who have abortions, but most pregnancies and abortions happen to women.

The US Supreme Court defied the court’s tradition and the expressed intentions of some of its members during their confirmation hearings by overturning the 50-year-old precedent, Roe v Wade, which had established abortion as a right. Immediately after the Dobbs v Jackson Women’s Health Organization decision was rendered on June 22, 2022, many states applied or enacted laws either severely limiting or banning abortion.

A week after the decision, a 10-year-old girl, pregnant by rape, was taken to Indiana, having been denied an abortion in her home state of Ohio. She was at high risk, not only for exacerbations of the trauma she had already experienced but for complications of pregnancy and childbirth, not to mention those of motherhood. It is notable, and relevant, that the first responses of Mike DeWine (Ohio’s governor), The Wall Street Journal, and other media was to declare that the story was untrue or could not be confirmed. No apologies were offered when the rapist was arrested and confessed. Next, the physician who performed the abortion was accused of not recording the procedure as required by law. When the girl’s evidence was produced, there was no apology or retraction. This is the country in which we now practice not only obstetrics and gynecology but also psychiatry. This is the country where our patients live.

Across the board, pregnancy leads to more danger of morbidity and mortality than abortion. Abortion is one of the safest procedures in all of medicine. One in 4 women in the United States will have an abortion during their lifetime. Before the Dobbs ruling, approximately 1 million abortions were performed in the United States each year. Clandestine, unsafe abortions deprive hundreds of thousands of children of the mothers who undergo those procedures. Abortion has been practiced throughout history and long before the advent of anesthesia and antibiotics. Perhaps the danger of abortion without those protections is the reason abortion is mentioned in the Hippocratic Oath. In any case, it means that abortions were happening in the fifth century BC.

In the United States, notably, the distribution of religious affiliations among women who have abortions is the same as that of the general population. Every day, women who oppose abortions have abortions—and many go on actively opposing abortions.

The terms commonly used to characterize positions for and against abortion are deeply prejudicial. In my opinion, pro choice likens a decision about a pregnancy to a choice between menu options or minor purchases. A decision about a pregnancy concerns the lives of the potential mother, the potential child, and many other individuals. All the evidence indicates that women consider abortion to be a serious decision. Pro life implies that individuals who have an abortion do not care about life. It is notable that the anti-abortion movement is completely divorced from any activism to support life other than that of a conceptus. It is not linked to concerns about war or the death penalty, not to mention the lives of children born into circumstances where their mothers doubt their ability to provide for and protect them (poverty, domestic violence, immaturity, the needs of other children). The terms pro choice and pro life carry misleading and damaging meanings. One positive effect of the Dobbs decision is the emergence of the word abortion from the shadows.

Commentators decrying abortion prohibitions are especially exercised about laws that do not make exceptions for rape and incest. Stop for a minute and consider the unescapable, excruciating assumptions that underlie those exceptions. Abortion opponents proclaim themselves to be protectors of the unborn. If the embryo or fetus is a human being, why should it be deprived of life because of circumstances over which it had no control? It is because the woman pregnant by rape or incest was not responsible for the sexual act that caused the pregnancy. Exceptions for

Research clearly demonstrates that although abortion is more likely in highly stressful life situations—which may include mental illness—abortion itself does not cause psychiatric illness; the most common response is relief.
Rape and incest lay bare the unspoken, unacknowledged belief that women who willingly engage in sex and become pregnant should be punished by having to stay pregnant. The punishment is usually rationalized by casting it as responsibility. It is twisted logic to consider that having a baby when one is not going to be able to care for it properly is responsible. It is twisted to make what, under good circumstances, is a blessing—a baby—into a punishment.

We are still operating under the conviction that the ills of society were caused by Eve eating the forbidden fruit in the Garden of Eden and then seducing Adam. But it does not work that way. Women with untenable pregnancies are unlikely to have conceived out of carefree unbridled lust—and what if they had?

Another unspoken assumption is that women have abortions because they do not care about children. In reality, they have abortions because they want to have wanted children—children they can provide for. In the United States, where sex education—if provided at all—may be full of misinformation, individuals sometimes become pregnant because they do not know how to avoid it.

There are all sorts of reasons women become pregnant under circumstances adverse for motherhood. They cannot afford contraceptives. Contraceptives fail. Their partners refuse to use condoms. Their partners force them to have unprotected sex. There are many ways to force sex on someone without committing what is legally defined as rape. Some women are living in violent relationships. Most women who have abortions already have children. Especially in the United States, which offers minimal—if any—parental leave and subsidized child care, adding another child would deprive the existing children of essential care and protection. Some women have psychiatric and/or other medical disorders that may prevent them from providing good maternal care.

What about the hidden part of the iceberg? The Dobbs decision leaves the country in a legal and clinical quagmire. On the basis of what I consider a ragbag of dubious constitutional arguments and false statements about the psychiatric sequelae of abortion, it removes the already attenuated protections of Roe v. Wade, leaving abortion’s legality to be decided by each of the 50 states. Some of the results are already apparent, and many others are expected. We have some forewarning about the implications because Catholic hospitals and inpatient parts of the country have already significantly limited care. Catholic (and evangelical) hospitals are not required to, and do not, inform patients that medical staff are not allowed to mention contraception or abortion. This prohibition also extends to psychiatrists at the hospitals.

In Catholic hospitals, women with incomplete spontaneous abortions, ectopic pregnancies, and fetuses with anomalies incompatible with intrauterine life are left to bleed, endure pain, and risk ectopic rupture rather than having their pregnancies terminated as medically indicated—as long as the clearly doomed fetus is considered to be alive. There are approximately as many spontaneous miscarriages each year as abortions. In many cases, it is impossible for a clinician to distinguish a miscarriage from an attempted abortion. Some of these laws will allow state officials to review medical records, question patients and doctors, and perhaps examine whatever tissue was removed in the hospital in an attempt to uncover an unlawful abortion.

We know that physicians in some places cannot obtain misoprostol, which has been approved for the treatment of serious medical conditions, because it is also used as an abortifacient. We know that many women have been tried in court, and some incarcerated, to punish them for behaviors that legal—not medical—practitioners have deemed deleterious to the fetus, including attempted suicide. In an illustrative case, a woman experienced a stillbirth at home. The authorities went through her computer and found that, at some point, she had searched for information about abortion pills. There was no evidence that she had ordered, obtained, or used them. The woman had to endure 3 years of anxiety before the case was dropped. We know that, although white women and women of color are equally likely to use street drugs while pregnant, poor, minority women are more likely to face these consequences.

As psychiatrists, we need to know the psychiatric aspects of abortion. Research clearly demonstrates that although abortion is more likely in highly stressful life situations—which may include mental illness—abortion itself does not cause psychiatric illness; the most common response is relief. Publications purporting to demonstrate psychiatric harm from abortion have been thoroughly and emphatically debunked because of unacceptable, biased, methodology. There is no evidence that abortion leads to later regret any more than any other life decision. There is, of course, a taboo against the expression of regret that one has had a child. Often, a woman who expresses regret about a past abortion, when asked to remember the circumstances at the time, will say that the abortion was the best option under those circumstances.

Many states have laws requiring a waiting period between the time a woman presents for abortion care and when the abortion is performed. This is a major hardship for women who have to travel to reach an abortion provider and provide coverage, if possible, for the absence from work and home. No other medical procedure, no matter how serious, requires a waiting period (except when there is a wait for available care). There is no evidence that abortion decisions are made on impulse. Abortion is similarly unique in being the subject of state laws mandating specific language that abortion providers must use with patients. This language generally conveys misinformation, including statements that abortion causes adverse psychiatric sequelae. Some laws require that a patient seeking abortion undergo—and view—ultrasound imaging of the embryo or fetus. Anti-abortion protesters outside abortion facilities, of course, cause distress. All these restrictions and mandates add stress to having an abortion.

Many states require that the parents of an underage girl be informed about or consent to her abortion. These laws seem like common sense; youngsters need parental guidance and support. But there is no evidence that mandated parental involvement is beneficial. Abortion providers will assist those who need help approaching their parents. Some girls realistically anticipate that their parents would punish or reject them if aware of their pregnancy—and/or force them to remain pregnant. The logic of mandated parental involvement is flawed. The situation is not difficult to understand; one will have a baby or one will not. The young woman deemed too immature to make the decision to abort will otherwise, in a few months, become the mother of an infant for whom she will have legal responsibility.

There is also the idea of fetal personhood.

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**Resources for Professionals and Patients**

The Guttmacher Institute: provides up-to-date information about abortion laws and statistics in the United States and all over the world

National Advocates for Pregnant Women: provides support and information for the public and pregnant women, whether they intend to abort or not; information about criminal cases against pregnant women and advocacy

Physicians for Reproductive Health: a group of clinicians who use evidence, training, and organized action to champion health care rights

American Civil Liberties Union: provides information about legal challenges to abortion restrictions

Planned Parenthood: provides access to care and resources

The impending crisis of access to safe abortion care in the US: This article includes a list of organizations that help patients find abortion care in a wide variety of ways. [https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2793700](https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2793700)
Many existing and pending state laws explicitly state that from the moment the sperm fertilizes the egg, that fertilized egg is entitled to all the legal rights of an individual. The conceptus, the embryo, the preivable fetus can only survive inside the body of a woman. Pregnant women may be made to undergo surgery or other inter-ventions aimed at improving the well-being of the fetus. This is a unique exception to American law, under which it is illegal to forcibly invade the body of a nonconsenting adult, even to remove 1 drop of blood that will save another person’s life. Many fertilized eggs are washed out of the body with menstrual blood, are resorbed, or otherwise disappear. How the states propose to protect fertilized eggs is unclear: when a law protecting them was passed in Indiana, protesting women sent used tampons to the state capitol.

Giving personhood to the unborn puts every woman who could become pregnant at risk of state investigation, control, intrusion, and prosecution. There are laws mandating that every woman seeking abortion care be registered in a state database, inviting intrusion and harassment not only by the state, but also by anti-abortion individuals or organizations. A Texas law, which is also under consideration elsewhere, offers $10,000 to any individual who identifies and sues someone who helps a woman obtain an abortion. Pharmacists are refusing to fill pregnant women’s prescriptions for clinically indicated medications, and oncologists are refusing to provide chemotherapy for pregnant women with malignancies. All these laws destroy the confidence and privacy of the doctor-patient relationship. Fetal personhood completely undermines the personhood of the pregnant woman.

At this moment, potential medical students and medical students planning to train as obstetrician-gynecologists have to decide whether to consider institutions in states where abortion is forbidden. Obstetricians are refusing care for women having spontaneous miscarriages and ectopic pregnancies for fear that they will be prosecuted for homicide. Firms placing ob/gyns in locum tenens positions find that prospects are unwilling to consider anti-abortion states.

Millions of women stand to lose ob/gyn care. Proposed and existing anti-abortion laws are so varied and often so ambiguous that there may be decades of litigation about them. For example, some states have proposed criminalizing travel from an anti-abortion state to another state to have an abortion. Is there not a right to travel freely between states? If there is not, what apparatus will states need to enforce such a prohibition—or will states rely on friends and neighbors to spy on and report one another? Some states propose to forbid mailing abortion medications to residents of their states. Can they legally control postal services? When challenges to these laws wend their way through the judicial system, they will arrive at the same Supreme Court that has just overturned the right to abortion.

The fate of in-vitro fertilization is also in doubt. When a woman’s ovaries are hyperstimulated to produce eggs, as many eggs as possible are harvested and fertilized to maximize the possibility of a successful pregnancy. Generally, they are genetically tested and those with abnormal genes are discarded—what if they are considered individuals with legal rights? As it is, state laws vary widely about control over frozen embryos. Infertility programs in some states have begun shipping their frozen embryos to “safe” states. Some will relocate their practices, leaving states that deem every embryo they create a human being entitled to state surveillance and protection. There reportedly has been a major increase in the number of men seeking vasectomies—which are often provided by untrained, nonmedical personnel—to demonstrate the heartbeat and any human-appearing features of the embryo or fetus. They dismiss concerns about circumstances and extol the joys of motherhood. They inform the woman that state laws require the father of a baby to provide for it, but they do not offer information about how rarely those laws are effective in the circumstances of the women they counsel. They exaggerate the support the state provides for mothers and babies. They attempt to delay the process in hopes that the pregnancy will progress beyond the abortion limit of the state. And they have an explicit policy of offering the bare minimum of support for the baby they hope the woman will have (a few diapers or something similar)—and they do not share this policy with those who are seeking help. Our patients may seek help at these centers.

So we now practice psychiatry, and teach medical students and residents, in a country with a patchwork of changing, ambiguous laws about abortion—some of which trample the cherished privacy of the doctor-patient relationship. Well-educated, financially able patients will continue to have access to abortions wherever they live; they can travel and are unlikely to get into trouble with the law. They will, however, continue to be at risk of dangerously delayed treatment for miscarriages and ectopic pregnancies—and of having fewer obstetricians in their states. Exceptions for the life of the mother are often interpreted to mean that, as long as the fetus is alive, despite having no chance of ultimate survival, the woman’s condition must deteriorate to the brink of death before her pregnancy is terminated.

Our most vulnerable patients in many states will lose their ob/gyn care. They will live in fear of a problem pregnancy and of government surveillance and criminal accusations. Some of our patients will be enraged and frightened by the Dobbs decision. We can help them strategize and to develop plans to protect themselves and those they care about. Our most vulnerable patients, if not pregnant at the moment, may be too preoccupied with the exigencies of their daily lives to focus on their loss of rights and care. Our responsibility is to know and communicate the facts and to help patients making pregnancy decisions review, consider, and act on their own values, beliefs, and circumstances.

The topic of abortion has 2 disadvantages. One is the general stigma of abortion, and the other is that individuals do not like to contemplate unpleasant, painful life possibilities. We like to believe that untenable pregnancies only happen to others. We often must help patients contemplate and plan for contingencies they would prefer to ignore, such as continuing to take medication even when they feel better. Now all our patients capable of becoming pregnant also need to be prepared to cope with a pregnancy that is untenable—for any reason. Perhaps everyone

All these laws destroy the confidence and privacy of the doctor-patient relationship.
who could become pregnant should be equipped with both Plan B—the “morning-after pill”—and a home medication abortion kit. Perhaps in some cases we will need to prescribe them.

Dr Stotland has a lifelong interest in psychosocial issues in women’s reproductive health. She is the editor or author of Psychiatric Aspects of Abortion and Abortion: Facts and Feelings, both published by the American Psychiatric Press. She has represented the American Psychiatric Association in testimony before the US Senate and Surgeon General and in several state courts about proposed and challenged laws related to abortion.

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

References
19. McGovern T. Overturning Roe v. Wade has had an immediate chilling effect on reproductive healthcare. BMJ. 2022;377:e6202.

Planning for Your 2022 Taxes

David Auer, CPA, MS, FPF, CGMA, and Medical Economics™ Staff

Taxes are inevitable, but proper planning can protect against an outsized portion of your income going to taxes. Recent changes to the tax code have made some past strategies outdated and new possibilities available. With inflation at the highest it has been in four decades, the need for physicians to utilize these strategies has gained outsized importance.

The first part of developing an effective tax strategy is determining which tax bracket you fall into and how much more you can earn before you move up to the next bracket. Based on experience, most doctors will find themselves paying around 35% and possibly up to 37%. If you have a C-corporation, the tax is a flat 21%, whereas self-employed physicians have a 12.4% and employed physicians have a 6.2% Social Security tax. Physicians should also factor in their capital gains taxes, as well as state income and corporate tax liability.

President Joe Biden has proposed increasing taxes, but legislators are running out of time to make the changes into law before the end of this year. Auer does not believe taxes on the highest earners will rise to the historical high of 49%. Depending on what state you live in and what other taxes you might be subject to, (your tax rate) could very well be into the 60% to 70% range, and that becomes very important when it comes to tax planning.

Doctors should maximize their retire- ment plan contributions, which lowers their taxable income and moves them to a lower tax bracket. Also consider a Roth conversion, which involves rolling over transferring funds from a traditional IRA or plan funds to a Roth IRA. This maneuver can be done by individuals who own a traditional IRA, a SEP IRA or those who have had a SIMPLE IRA for at least 2 years. It is also available to those with a 401(k), 403(b), or a government 457(b) plan eligible for distribution. Roth IRA funds can be withdrawn tax-free so long as the funds have been held for at least 5 years and the holder is at least 59.5 years. There is also no lifetime required minimum distributions for Roth IRA owners.

Also considering funding a “back door” Roth IRA and a Mega Roth 401(k) to further lower taxable income. If properly utilized, these can enable physicians to put away an additional $6,000 and lower their taxable income. When it comes to investments, harvesting capital losses is a good plan, as it can offset current and future capital, plus an addition $3,000 a year. However, beware of the capital wash rules that say you cannot buy the same assets, which leads to the initial loss for 30 days.

Physicians should also consider converting W-2 income to 1099 income either in part or entirety. This is helpful, especially if the physician has locum tenens income in addition to their regular job. This also adds the ability to claim business expenses as deductibles.

For those physicians who already have Schedule C/1099 income, consider converting that income to an S-Corporation LLC. This will lower yourself-employment taxes and reduce the risk of an audit. Based on the most recent published statistics the IRS has provided, generally speaking, if you have a Schedule C income of over $250,000, you currently have about a 2.5% chance of an IRS audit. If you have that same income going through an S-Corporation, statistically, that drops your audit risk down to 0.7%—a fairly significant drop in the risk of an audit, everything else being the same.

With an S-Corporation in place, consider employing family members by putting them on the payroll and assign- ing responsibilities. This shifts income from being subject to your tax bracket to being subject to their tax bracket. A physician can also maximize their home office and automobile deductions. There are acceptable ways to do this, physicians should work with a tax planner to ensure they are getting the most out of the vehicle and workspace. Physicians should also consider the per diem allowances for lodging and meals as opposed to the actual expenses. Finally, physicians should consider making a pass-through entity (PTTE), such as an S-Corporation or partnership, to pay individual state income taxes at the PTPE level, which enables the clinician to deduct the cost of that tax dollar for dollar. This is available in 40 states.

Mr Auer is the president and founder of Physician Tax Solutions.
CASE STUDY

"Mr Wright" is a 37-year-old man with no medical comorbidities who has been in the United States for more than 10 years. He presented to primary care with a 4-month history of headaches that were unresponsive to over-the-counter nonsteroidal anti-inflammatory drugs (NSAIDs). He is started on amitriptyline 25 mg at bedtime daily and is referred to the psychiatry department for "anxiety" without any further notes on symptoms of anxiety. The patient is worried he will be labeled "crazy" and is upset that his suffering is not being taken seriously.

He appears to be in good physical health with good grooming, although he is somewhat reluctant during the psychiatric interview. He reports that he has been living with his wife and child, and he works at a restaurant. He has teenaged children who do not live with him, but he reportedly has a good relationship with them.

When describing his headaches, Mr Wright relays that they persist all day long and encompass areas around his bilateral temples and occipital area, although the pain may migrate between these areas. He has tried lying down to rest, but finds it useful, but cannot get relief from headaches. He stretches his neck in a variety of different angles during our interaction to help relieve the pain, along with some excess eye blinking that he seems unaware of. He denies a premonitory sensation occurring prior to his movements.

After repeated queries into his stressors around the time his headaches started, Mr Wright is able to verbalize an incident that occurred a week before their onset. He was accommodating his sister at his home after an interpersonal conflict with her husband. The brother-in-law had held him at gunpoint outside his home. He ran inside to safety and the brother-in-law eventually left. His sister has since left, and the patient feels that the turmoil of an abusive relationship in his sister’s life is persistent and acceptable to his sister and the rest of the family. He recalls a similar event more than 20 years ago when he was chased by a different family member in his home country. At that time, Mr Wright also felt that his life was in danger and had to run to safety; since then, he has been an anxious person in general. He has never received any mental health treatment (including psychotherapy).

He denies typical symptoms of posttraumatic stress disorder (PTSD), including nightmares, flashbacks, and avoidance of increased arousal.

A chart review shows that Mr Wright was seen in the emergency department twice since meeting with his primary care provider. On one occasion, he had acute chest pain; negative EKG and cardiac enzymes led to a discharge. On the second occasion, he was evaluated for unprotected sexual contact with an unknown individual. Mr Wright had chosen not to mention either of these instances of his interaction with the medical system, and the psychiatrist chose not to discuss them either.

He was started on amitriptyline 25 mg by his primary care physician 2 weeks ago, and has been using it as needed on nights he is unable to sleep. He finds it useful, but cannot get relief from headaches. He is unable to verbalize any correlation between a life-threatening event and the onset of his headaches.

At the conclusion of the visit, both patient and physician agree that the amitriptyline should be continued, but that the patient should take it more regularly for best therapeutic results.

Discussion

As per a systematic review of a global burden of disease across the United States, in 2017, the 5 highest incidence rates of neurological diseases included migraines and tension-type headaches. Migraines have consistently been among the top 3 neurological diseases in terms of disability-adjusted life years. As a testament to how frequently psychiatrists and neurologists see patients with headaches and psychiatric diagnoses, in 2019, the most frequent psychiatric comorbidities in individuals with primary headaches in the United States were anxiety and depression, followed by posttraumatic/stressor and trauma-related stress disorder. These comorbidities are found in 25%, 23%, and 15% of the general population, respectively.

It is inevitable then that one is likely to come across patients with both primary and secondary headaches in psychiatric practice. Recognizing headaches can be a powerful tool in evaluating the quality of life of our patients. Headaches can be triggering and perpetuating factors for psychiatric conditions, in addition to being an important consideration in identifying the best pharmacological options for treatment.

Biopsychosocial Model

In primary headaches such as migraine and tension headaches, there is no source for nociceptive activity such as a hemorrhage or inflammation. Many theories have tried to explain the connections between distress and primary headaches. Findings from studies on connections between distress and primary headaches clearly show that the most important triggering events for primary headaches are distress and sleep issues. Stress has also been linked with the transformation of episodic migraines to chronic migraines that carry a greater burden of disease. Interestingly, repeated exposure to trauma, even without a formal PTSD diagnosis, is prominent in adults with chronic migraine headaches as compared with healthy adults without migraines.

Biopsychosocial factors are believed to be involved in headache perception. Transactional models propose that the mismatch between threat perception and capability to deal with the threat can be applied to the subjective sense of pain in migraines, as well as to any other pain syndrome. Among personality traits, locus of control being perceived...
as internal versus external is a predictor of better headache outcomes. During the COVID-19 pandemic, the role of sudden change in psychosocial environment due to shutdowns among those with preexisting migraines has been investigated. Contrary to the impression that headaches would worsen, results from at least 1 study record improvement. The findings document reduction in migraine intensity and frequency in adults during the shutdown in Italy in 2020. It is reasonable to speculate that the reduction in academic and social pressures were helpful in this improvement and underscore the role of psychosocial intervention in patients with migraines. Moreover, it would be interesting to see if there is an uptick in migraine presentation to neurologists and psychiatrists due to the chronic stress induced by the pandemic, over and above migraine in individuals caused by the neuropsychiatric effects of COVID-19 infection itself.

Neuropsychiatry of Headache
Migraine headaches have a bidirectional relationship with a spectrum of psychiatric illnesses, the strongest correlation being with depression, anxiety, and bipolar disorder. There is evidence of shared genetic predisposition, as well as functional and structural alterations in pain-modulating brain areas, including the amygdala, anterior cingulate cortex, and periaqueductal gray in both migraine and affective disorders. Moreover, they share similar abnormalities in the HPA axis as well as common mechanisms of action of treatment modalities.

The concept of central sensitization is often used to explain pain-related conditions, including migraine. Patients with chronic migraines (as compared with episodic migraines) have more somatic complaints. The role of pain sensitization in episodic migraines has also been investigated in episodic migraines. A recent study suggested that slowly repeated evoked pain sensitization could in fact be useful as a clinical predictor for episodic migraines.

Serotonin, norepinephrine, and the GABAergic system have all been implicated in the etiology of psychiatric as well as primary headaches at the system have all been implicated in the etiology of the chronic pain. More specifically, SNRIs and TCAs have been implicated in the etiology of the anterior cingulate cortex, and periaqueductal gray functional and structural alterations in pain-modulating brain areas, including the amygdala, anterior cingulate cortex, and periaqueductal gray in both migraine and affective disorders. Moreover, they share similar abnormalities in the HPA axis as well as common mechanisms of action of treatment modalities.

The concept of central sensitization is often used to explain pain-related conditions, including migraine. Patients with chronic migraines (as compared with episodic migraines) have more somatic complaints. The role of pain sensitization in episodic migraines has also been investigated in episodic migraines. A recent study suggested that slowly repeated evoked pain sensitization could in fact be useful as a clinical predictor for episodic migraines.

Pearls in Management
Managing psychiatric symptoms in patients presenting for treatment with headaches may present a unique advantage in overcoming barriers to talking about optimizing mental health. When establishing goals for treatment, it may be useful to educate the patient about the benefit of SNRIs and TCAs in managing headaches as well as mood and anxiety disorders. This may help patients verbalize their mental health needs in the face of stigma. At times, presenting an SNRI or TCA as a headache medicine only can help with treatment adherence in patients who have difficulty expressing their distress.

One of the many challenges in managing headaches is that initiating SNRIs or TCAs for headache can itself carry a risk for inducing headaches. A careful consideration of the timeline for medication-induced headache may aid in separating the superimposed symptoms. Clinicians may benefit from considering medication withdrawal as a reason for headache exacerbation when treating psychiatric patients with comorbid headaches and a history of nonadherence. Venlafaxine is notable in this regard for its withdrawal syndrome.

Investigators of several studies have been unable to establish the benefit of using selective serotonin reuptake inhibitors (SSRIs) in preventing migraine relapses. Among the most studied SSRIs is fluoxetine, which, to date, has conflicting evidence for its use in primary headaches. Other clinical trials of serotonin and norepinephrine did not show benefit over placebo. Hence, when a patient with previously established treatment with SSRIs is placed on TCAs for headaches, one has to carefully weigh the risks and benefits of switching to monotherapy with a TCA or continuing with both medications. If the patient is reporting clinical benefit, they could be treated with low doses of both medication categories while monitoring carefully for adverse effects. Patients can be educated regarding early symptoms of serotonin syndrome when treated in the outpatient setting.

Additionally, many clinicians are concerned about the possibility of inducing serotonin syndrome in patients taking antidepressants who are prescribed triptans for aborting episodes of migraines. Although there was a black box warning for this interaction, results from an electronic health record–based study in 2018 did not show any correlation of serotonin syndrome with co-use of SSRIs and SNRIs and triptans.

In patients with medication-overuse headaches, the prevalence of psychiatric comorbidities is even higher. Some point to the similarities between compulsive medication intake for episodes of migraine and obsessive-compulsive disorder. As such, adding behavioral interventions for this subset of patients may be highly effective in improving headache outcomes.

It may be prudent for neurologists to prescribe psychotherapy regularly for treating patients with chronic migraines. Behavioral interventions and forecasting models, including stress variables, seem to be useful in managing migraine. Behavioral treatments with evidence for migraine prevention include stress management, relaxation therapy, cognitive behavioral therapy, biofeedback, mindfulness-based therapies, and acceptance and commitment therapy. Investigators of some studies point out that although headache frequency intensity improves, there is no change in physiological markers of headaches such as muscle tension. In a landmark study of electromyographic biofeedback training, participants viewed their headaches as having a more internal locus of control and themselves as more self-efficacious (ie, as capable of influencing their headaches) following treatment.

Presenting an SNRI or TCA as a headache medicine only can help with treatment adherence in patients who have difficulty expressing their distress.

Concluding Thoughts
Finally, when addressing this complex patient population, it is essential to avoid labeling and stigmatization. Patients are usually concerned about physical complaints being dismissed and being told “the symptoms are in your head.” Establishing careful therapeutic rapport goes a long way toward open discussions of treatment options and paving the way to productive illness management.

Dr Shamim is a psychiatrist in Houston, Texas.

References
Using Cognitive Behavioral Therapy to Enhance Well-Being

Robert Hindman, PhD

Cognitive behavioral therapy (CBT) has traditionally focused on alleviating symptoms of psychiatric disorders in addition to helping patients solve life problems. CBT practitioners illustrate this by monitoring therapeutic progress through symptom measures related to the psychiatric diagnosis (e.g., Beck A. M. D., 2013).

For patients 6 years and older with Attention Deficit Hyperactivity Disorder

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INDICATION

DYANAVELO XR is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years and older.

IMPORTANT SAFETY INFORMATION

WARNING: ABUSE AND DEPENDENCE

- CNS stimulants, including DYANAVELO XR, other amphetamine-containing products, and methylphenidate, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy.

- DYANAVELO XR (amphetamine) is contraindicated in patients known to be hypersensitive to amphetamine, or other components of DYANAVELO XR. Hypersensitivity reactions, such as angioedema and anaphylactic reactions, have been reported with other amphetamines.

- DYANAVELO XR is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs), or within 14 days of stopping MAOIs, because of increased risk of hypertensive crisis.

- Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmia, coronary artery disease, and other serious heart problems. Sudden death, stroke, and myocardial infarction have been reported in adults with CNS stimulant treatment at recommended doses. Sudden death has been reported in pediatric patients with structural cardiac abnormalities and other serious heart problems taking CNS stimulants at recommended doses for ADHD. Further evaluate patients who develop exertional chest pain, unexplained syncope, or arrhythmias during DYANAVELO XR treatment.

- CNS stimulants cause increase in blood pressure (mean increase about 2 to 4 mm Hg) and heart rate (mean increase about 3 to 6 bpm). Monitor all patients for tachycardia and hypertension.

- CNS stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a preexisting psychotic disorder. They may induce a mixed/manic episode in patients with bipolar disorder prior to initiating treatment. At recommended doses, stimulants may cause psychotic or manic symptoms, e.g., hallucinations, delusional thinking, or mania, in patients without prior history of psychotic illness or mania. If such symptoms occur, consider discontinuing DYANAVELO XR (amphetamine).
Anxiety Inventory, Beck Depression Inventory).1 Research on CBT outcomes generally use the same measures to determine treatment efficacy or effectiveness. CBT has gained a robust research literature demonstrating its ability to reduce symptoms of distress in multiple psychiatric disorders.2 Nevertheless, it has been argued that a greater focus is needed on enhancing overall well-being.3 This argument is not new, and many fields of psychology focus on overall well-being. The field of positive psychology was founded on the premise that it takes different types of interventions to enhance positive emotional states than to alleviate distress.3 For example, practitioners of positive psychology may help patients identify their signature strengths and find ways to use those strengths in daily life. Patients also can learn how to enhance positive emotional states by interventions aimed at increasing their sense of gratitude. Enhancing well-being also has been incorporated into “third wave” treatments such as acceptance and commitment therapy, which includes values as a central component of treatment.4 Patients learn how to identify their values and live according to their values as opposed to being guided primarily by their thoughts or emotions.

Recently, CBT has shifted to include a greater emphasis on enhancing...

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- CNS stimulants have been associated with weight loss and slowing of growth rate in pediatric patients with ADHD; monitor weight and height during treatment with DYANAVEL XR (amphetamine). Treatment may need to be interrupted in children not growing as expected.
- CNS stimulants, including DYANAVEL XR, are associated with peripheral vasculopathy, including Raynaud’s phenomenon. Signs and symptoms are usually intermittent and mild; very rare sequelae include digital ulceration and/or soft tissue breakdown. Careful observation for digital changes is necessary during treatment with ADHD stimulants.
- Serotonin syndrome risk is increased when co-administered with serotonergic agents (e.g., SSRIs, SNRIs, triptans), MAOIs, and during overdosage situations. If it occurs, discontinue DYANAVEL XR and any concomitant serotonergic agents immediately, and initiate supportive treatment.
- Most common adverse reactions observed with amphetamine products: dry mouth, anorexia, weight loss, abdominal pain, nausea, insomnia, restlessness, emotional lability, dizziness, and tachycardia. Based on limited experience with DYANAVEL XR in controlled trials, the adverse reaction profile of DYANAVEL XR appears similar to other amphetamine extended-release products. The most common (≥2% in the DYANAVEL XR group and greater than placebo) adverse reactions reported in the Phase 3 controlled study conducted in 108 patients with ADHD (aged 6 to 12 years) were epistaxis (DYANAVEL XR 4%, placebo 0%), allergic rhinitis (4%, 0%) and upper abdominal pain (4%, 2%).
- DYANAVEL XR (amphetamine) use during pregnancy may cause fetal harm.
- Breastfeeding is not recommended during treatment with DYANAVEL XR.

Please see Brief Summary of Prescribing Information, including Boxed Warning regarding Abuse and Dependence, on the following pages.

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*Terms and Conditions apply.
ER, extended-release; IR, immediate-release.

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An Illustrative Case Example

“Henry” is a recently retired high school teacher who was referred to treatment by his primary care physician because of complaints about elevated anxiety and an overall depressed mood. He grew up in a household with a physician father who was dedicated to his job and rarely home as a result. Both parents stressed the importance of learning and hard work. For instance, as a child, Henry was not allowed to watch television programs, as it was considered “being lazy.” Henry’s parents also criticized him for not performing at the top of his class, a result of his undiagnosed attention-deficit/hyperactivity disorder. He tried to please his parents different times and at therapeutic doses in all age groups throughout the course of treatment. Signs and symptoms generally improve after reduction in dose or discontinuation of drug. Careful observation for digital changes is necessary during treatment with ADHD stimulants. Further clinical evaluation (e.g., psychomotor referral) may be appropriate for certain patients.

Serotonin Syndrome: Serotonin syndrome, a potentially life-threatening reaction, may occur when amphetamines are used in combination with other drugs that affect the serotonergic neurotransmitter system. Such drugs include monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonin receptor antagonists (SNRIs), triptans, tricyclic antidepressants, fentanyl, tramadol, zopiclone, bupropion, and St. John’s Wort. The concomitant administration with cytochrome P450 2D6 (CYP2D6) inhibitors may also increase the risk with increased exposure to Dyanavel XR. In these situations, consider an alternative non-serotonergic drug or an alternative drug that does not inhibit CYP2D6. In addition, the syndrome may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, hyperreflexia, incoordination), laboratory findings including temperature elevation, diaphoresis, tachycardia, hyponatremia, and hyperreflexia. Discontinue treatment with Dyanavel XR and the CYP2D6 inhibitor may lead to addiction, and some individuals may develop dependence even when taking Dyanavel XR as prescribed. Signs of physical dependence may occur upon abrupt discontinuation, including sleep disturbances, anxiety, dysphoria, depression, tremor, or irritability. Patients who are not growing or gaining height or weight as expected may need to have their height and weight monitored and their dose adjusted or other treatment measures instituted if clinical signs of hypothyroidism are present. Dyanavel XR is contraindicated: (a) in patients known to be hypersensitive to amphetamine or other components of Dyanavel XR, hypersensitivity reactions such as angioedema and anaphylactic reactions have been reported in patients treated with other amphetamine products; (b) in patients taking monoamine oxidase inhibitors (MAOIs), within 14 days of stopping MAOIs, because of an increased risk of hypertensive crisis.

Warnings and Precautions

Potential for Abuse and Dependence: CNS stimulants, including Dyanavel XR, other amphetamine-containing products, and methylphenidate, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy.References:

“Human” is a recently retired high school teacher who was referred to treatment by his primary care physician because of complaints about elevated anxiety and an overall depressed mood. He grew up in a household with a physician father who was dedicated to his job and rarely home as a result. Both parents stressed the importance of learning and hard work. For instance, as a child, Henry was not allowed to watch television programs, as it was considered “being lazy.” Henry’s parents also criticized him for not performing at the top of his class, a result of his undiagnosed attention-deficit/hyperactivity disorder. He tried to please his parents different times and at therapeutic doses in all age groups throughout the course of treatment. Signs and symptoms generally improve after reduction in dose or discontinuation of drug. Careful observation for digital changes is necessary during treatment with ADHD stimulants. Further clinical evaluation (e.g., psychomotor referral) may be appropriate for certain patients.

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and avoid criticism by dedicating more time to schoolwork than his peers, which led him to neglect his social life.

Henry reportedly fairly consistent anxiety throughout his life, mainly related to his academic and later his work performance, as well as to how other people viewed him. He noted a prior untreated episode of depression, which occurred when he was graduating from college and was not accepted into any of the graduate school programs to which he applied. He originally planned on becoming a professor but decided on a career as a high school teacher, as he did not believe he would ever be able to get into an adequate graduate program. His second major depressive episode began about 3 months after he retired. Since becoming depressed, Henry became more withdrawn, and has spent most of his time on the couch watching news programs. The focus of his worry was whether he would be able to enjoy retirement and what the rest of his life would involve. Henry met diagnostic criteria for major depressive disorder and recurrent, moderate, and generalized anxiety disorder.

Treatment Components

Goal setting is an important component in beginning CBT. Traditionally, the focus of CBT is to identify and challenge dysfunctional beliefs and develop new coping strategies. In this case, Henry’s beliefs about his academic and work performance were identified as a major contributor to his anxiety and depression. Henry was encouraged to challenge these negative beliefs and develop more adaptive thinking strategies. He was also provided with strategies to manage his anxiety symptoms, such as deep breathing and mindfulness techniques. Henry was also encouraged to set realistic goals and break them down into smaller, manageable steps. He was taught to recognize and challenge his perfectionistic thinking patterns and to develop more realistic and flexible goals. Henry was also given homework assignments to practice these skills in his daily life. Henry was encouraged to continue working on these skills outside of therapy and to report his progress to the therapist at each session. Henry was also encouraged to continue working on his goals and to report his progress to the therapist at each session. Henry was also given homework assignments to practice these skills in his daily life. Henry was encouraged to continue working on these skills outside of therapy and to report his progress to the therapist at each session.
treatment goals focus on resolving life problems as well as symptom reduction or management. When I asked Henry what he wanted to accomplish in therapy, Henry initially listed these goals: “Get out of this depression,” “stop worrying so much,” and “enjoy retirement.” Goal setting with clients should involve choosing specific goals that have measurable outcomes. Accordingly, I asked Henry what he would be doing differently—or how his life would be different—if he were not depressed, if he stopped worrying, and if he was enjoying retirement. Henry was able to come up with more specific behavioral goals: “Go on daily walks,” “read for fun,” and “complete more woodworking projects.”

Instead of stopping at standard CBT goals, I decided to determine whether we could set additional goals to enhance Henry’s overall sense of well-being. We accomplished this by first assessing his values. I read through different potential values and asked him to rate on a scale of 0 to 10 (0 = no value at all; 10 = the most something can be valued) how important each value was to him. The areas of value we covered were: work/career; learning; volunteering; intimacy; friendship; family; recreation; and health. I then asked Henry to look at his rated values and see if there was a discrepancy between what he valued and how he was living his life. We were then able to develop additional values-based treatment goals of: “developing and maintaining better friendships,” “developing joint interests/hobbies with my wife,” and “finding ways to contribute to society in retirement.”

Standard CBT treatment for a withdrawn, depressed patient begins with behavioral activation. Behavioral activation is aimed at helping depressed patients become more active and engaged in life by scheduling specific activities throughout the week. These activities allow the patient to have pleasurable experiences and to cut down on time spent ruminating. Traditionally, CBT practitioners help patients identify activities that give them either a sense of pleasure or a sense of accomplishment. For instance, watching a movie might be pleasurable, while exercising can lead to a sense of accomplishment.

To have a greater focus on enhancing well-being instead of solely alleviating depression, we used values-based activities for behavioral activation. Henry decided to schedule a daily walk with his wife, which was consistent with his values of connecting with his wife and helping her reach her health goals, as well as his own desire to live a healthier life. In line with his value of learning, he also signed up for a weekly woodworking class. Between classes, he decided to dedicate 2 days per week to using the skills he learned on his own woodworking projects, which was related to his work/career value of being productive. Lastly, Henry wanted to enhance the friendships he had neglected for most of his career due to his taking on an excess of work tasks. He was able to focus on his value of friendship by contacting a few existing friends; he set up a weekly lunch date with one and joined another friend’s cycling group.

After focusing on these activities for about 1 month, Henry’s major depressive episode resolved, but he still reported lacking an enhanced sense of well-being. We determined a few factors were getting in the way of his sense of well-being. The first was his deeply entrenched drive to be productive that he had learned from his parents. Initially, I used the standard CBT strategy of cognitive restructuring through Socratic questioning to try to help him determine that his
current activities could be viewed as being productive. For instance, going on walks with his wife was productive for his own health and for enhancing his connection with his wife. Despite this, he still held on to the idea that productivity was work related and kept going back to the fact that his father had dedicated his life to his work and chosen not to retire. Instead of trying to help Henry change his view on work, I defined productivity as an important value of his. We then focused on how to include productivity in his life, and Henry came upon the solution of volunteering as a tutor 2 days per week. By volunteering, Henry was able to satisfy his treatment goal of finding ways to contribute to society in retirement.

The second factor interfering with Henry’s sense of well-being was worry. He reported that his current worries centered on how other people viewed him and whether he was enjoying retirement as much as he should. We started worry reduction of his social fears through the standard CBT strategies of Socratic questioning for cognitive restructuring of his worry thoughts and evaluating positive (worry is helpful) and negative (worry is uncontrollable and potentially harmful) beliefs about worry itself. In using cognitive restructuring for his social worries, Henry was able to realize that he likely did not give as negative of an impression as he imagined and that people tended to respond positively to him when he made an effort to converse. He also came to the conclusions that he cannot know for certain what other people think of him and he cannot control how others view him overall.

Given these conclusions, we then focused on what Henry was able to control (ie, his behavior). Attempting to enhance his sense of well-being, I asked Henry how he valued acting well toward others. He determined that he valued being kind, supportive, a good listener, and more outgoing. We then concretely defined what this would look like in his weekly social interactions and role-played example social interactions during sessions. He was then able to act more in accordance with his social values.

The last component we focused on was Henry’s worry that he was not enjoying retirement as much as he should. Throughout his career, Henry had heard his fellow teachers discuss how amazing retirement was going to be and would hear from those who had retired about how happy they were. As a result, Henry was constantly evaluating his emotional experience and thinking that he should be feeling happier in his day-to-day life. For instance, he would be completing a woodworking project, note he felt happiness at a 5/10 level, and believe he should be enjoying the project more, which would then cause his happiness to dip to a 2/10 level. Through these experiences, I helped him determine that both evaluating his sense of happiness and wanting to increase his experience of happiness tend to backfire and lead to less happiness. I also helped him come to the realization that he is not able to control his emotional state at will. I asked him to recount the last time he experienced at least a moderate amount of happiness, and whether he was focused on analyzing what was happening and how it was making him feel. He noted that he was not focused on analyzing his level of happiness at all; he was just fully engaged in the experience and even lost a sense of himself to a degree.

I guided Henry through a mindfulness exercise to strengthen his ability to notice his emotional state and related thoughts without getting caught up in them or trying to control them, while also becoming fully absorbed in the experiences around him. Henry then practiced taking this approach to his day-to-day valued experiences. He came up with the saying, “If I’m a 5 (happiness level), I can let myself be a 5.” Henry reported this intervention as being the most important in enhancing his sense of well-being, as he was able to “get out of [his] head” and experience life to the fullest.

Concluding Thoughts

CBT has traditionally focused on alleviating symptoms of psychiatric disorders and resolving problems, but it has recently included a greater focus on living a valued life and enhancing well-being. A CBT approach focused on enhancing well-being continues to include goal setting, problem solving, and standard CBT cognitive strategies such as cognitive restructuring and Socratic questioning, as well as behavioral strategies including behavioral activation and exposure exercises. Nonetheless, throughout the course of treatment, patients are encouraged to identify their values, live according to their values, and become fully engaged in valued experiences. Through a greater emphasis on valued experiences, well-being can be enhanced in addition to distress being alleviated.

Dr Hindman is a licensed clinical psychologist at the Beck Institute for Cognitive Behavior Therapy in Bala Cynwyd, Pennsylvania.

References


Dr Berlin has been writing a poem about his experience of being a doctor every month for the past 24 years in Psychiatric TimesTM the “Poetry of the Past 24 Years” column. He is instructor in psychiatry, University of Massachusetts Medical School, Worcester, Massachusetts. His latest book is Freud on My Couch.
CAPLYTA is indicated in adults for the treatment of schizophrenia and depressive episodes associated with bipolar I or II disorder (bipolar depression), as monotherapy and as adjunctive therapy with lithium or valproate.

**Important Safety Information**

**Boxed Warnings:**

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

- **Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric and young adults in short-term studies.** Closely monitor all antidepressant-treated patients for clinical worsening, and for emergence of suicidal thoughts and behaviors. The safety and effectiveness of CAPLYTA have not been established in pediatric patients.

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

**Warnings & Precautions:** Antipsychotic drugs have been reported to cause:

- **Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis**, including stroke and transient ischemic attack. See Boxed Warning to the left.

- **Neuroleptic Malignant Syndrome**, which is a potentially fatal reaction. Signs and symptoms include hyperpyrexia, muscle rigidity, delirium, autonomic instability, elevated creatinine phosphokinase, myoglobinuria (and/or rhabdomyolysis), and acute renal failure. Manage with immediate discontinuation of CAPLYTA and provide intensive symptomatic treatment and monitoring.

- **Tardive Dyskinesia (TD),** a syndrome of potentially irreversible, dyskinetic, and involuntary movements which may increase as the duration of treatment and total cumulative dose increases. The syndrome can develop after a relatively brief treatment period, even at low doses, or after treatment discontinuation. Given these considerations, CAPLYTA should be prescribed in a manner most likely to reduce the risk of TD. Discontinue CAPLYTA if clinically appropriate.

- **Metabolic Changes,** including hyperglycemia, diabetes mellitus, dyslipidemia, and weight gain. Hyperglycemia, in some cases extreme and associated with ketoacidosis, hyperosmolar coma or death, has been reported in patients treated with antipsychotics. Measure weight and assess fasting plasma glucose and lipids when initiating CAPLYTA and monitor periodically during long-term treatment.
Choose CAPLYTA
for a broad range of adults with bipolar depression¹

- Proven efficacy in bipolar depression (bipolar I and II)*
- Once-daily, titration-free dosing—patients start on the effective dose
- Broad access
- Changes in weight and akathisia were similar to placebo at week 6¹
- Antipsychotic drugs have been reported to cause metabolic effects and tardive dyskinesia

Please see Important Safety Information below.

*Based on the Montgomery-Asberg Depression Rating Scale (MADRS) total score at week 6.

- Leukopenia, Neutropenia, and Agranulocytosis (including fatal cases). Perform complete blood counts in patients with pre-existing low white blood cell count (WBC) or history of leukopenia or neutropenia. Discontinue CAPLYTA if clinically significant decline in WBC occurs in absence of other causative factors.

- Orthostatic Hypotension and Syncope. Monitor heart rate and blood pressure and warn patients with known cardiovascular or cerebrovascular disease. Orthostatic vital signs should be monitored in patients who are vulnerable to hypotension.

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

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

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

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

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

Drug Interactions: Avoid concomitant use with CYP3A4 inducers. Reduce dose for concomitant use with strong CYP3A4 inhibitors (10.5 mg) or moderate CYP3A4 inhibitors (21 mg).

Special Populations: Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. Breastfeeding is not recommended. Reduce dose for patients with moderate or severe hepatic impairment (21 mg).

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

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

CAPLYTA is available in 42 mg capsules.

Please see the accompanying Brief Summary of Prescribing Information on the following pages.

Reference: 1. CAPLYTA prescribing information, 2022.
CAPLYTA is contraindicated in patients with history of hypersensitivity reaction to lumateperone. Reactions have recommended dosage for patients receiving moderate CYP3A4 inhibitors is CAPLYTA 21 mg once daily. or valproate. CAPLYTA is indicated for the treatment of schizophrenia in adults and depressive episodes associated with bipolar I or II disorder (bipolar depression) in adults, as monotherapy and as an additive therapy with lithium or valproate.

**DOSAGE AND ADMINISTRATION**

**Recommended Dosage:** The recommended dosage of CAPLYTA is 42 mg administered orally once daily or without food. Dose titration is not required.

**Dosage Recommendations for Concomitant Use with Moderate or Strong CYP3A4 Inhibitors:** Concomitantly administered with strong CYP3A4 inhibitors. The recommended dosage for patients receiving strong CYP3A4 inhibitors is CAPLYTA 10.5 mg once daily. Concomitantly administered with moderate CYP3A4 inhibitors. The recommended dosage for patients receiving moderate CYP3A4 inhibitors is CAPLYTA 21 mg once daily.

**Contraindications**

CAPLYTA is contraindicated in patients with history of hypersensitivity reaction to lumateperone. Reactions have included pruritus, rash (e.g., allergic dermatitis, papular rash, and generalized rash), and urticaria.

**WARNINGs AND PRECAUTIONS**

**Increased Mortality in Elderly Patients with Dementia-Related Psychosis:** Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials in elderly patients taking typical antipsychotic drugs, revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in placebo-treated patients. Although the causes of death were not all observed, most deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. CAPLYTA is not approved for the treatment of patients with dementia-related psychosis.

**Suicidal Thoughts and Behaviors**

In placebo-controlled trials in elderly patients with dementia-related psychosis, antidepressants increased the risk of suicidal thoughts and behaviors in pediatric and young adult patients (age less than 18) in placebo-controlled trials of antidepressants in children and adolescents. A positive association was observed in short-term, 4- to 6-week, trials with a risk of suicidal thoughts and behaviors in patients with a recent history of myocardial infarction (ischemic heart disease, heart failure, or conduction abnormalities), and patients with cerebrovascular disease. CAPLYTA has not been evaluated in patients with a recent history of myocardial infarction or cerebrovascular disease. CAPLYTA has not been evaluated in patients with a recent history of a myocardial infarction or cerebrovascular disease. CAPLYTA has not been evaluated in patients with a recent history of myocardial infarction or cerebrovascular disease. In placebo-controlled trials of adult patients with schizophrenia, mean changes from baseline and the proportion of patients with shifts to normal ≥ 7% from baseline to end of study was 12%, respectively. 4.7% of patients with normal hemoglobin A1c (<6.5%) at baseline developed elevated levels of fasting total cholesterol and triglycerides were similar in patients treated with CAPLYTA and placebo. In an uncontrolled open-label trial of CAPLYTA for up to 1 year in patients with stable schizophrenia, the percentages of patients with a shift from normal to high were 15%, 5%, and 2% for total cholesterol, triglycerides, and LDL cholesterol, respectively.

**Bipolar Depression**

In an uncontrolled open-label trial of CAPLYTA for up to 6 months in patients with bipolar depression, the proportions of patients with a shift from normal to high were 15%, 5%, and 2% for total cholesterol, triglycerides, and LDL cholesterol, respectively.

**Weight Gain**

Weight gain has been observed with use of antipsychotics. Monitor weight at baseline and following treatment at regular intervals. CAPLYTA is not indicated for the treatment of patients with dementia-related psychosis.

**Pregnancy:** Pregnancy Exposure Registry - CAPLYTA has been linked to the formation of aniline metabolites of lumateperone
**Body Temperature Dysregulation**: Atypical antipsychotics may disrupt the body's ability to reduce core body temperature. Strainous exercise, exposure to extreme heat, dehydration, and anticholinergic medications may contribute to an elevation in core body temperature; use CAPLYTA with caution in patients who may experience these conditions.

**Dysphagia**: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Antipsychotic drugs, including CAPLYTA, should be used cautiously in patients at risk for aspiration.

**ADVERSE REACTIONS**

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

The most common adverse reactions (incidence of at least 5% of patients exposed to CAPLYTA and greater than twice the rate of placebo) were somnolence/sedation and dry mouth.

**Tardive Dyskinesia**: The risk of tardive dyskinesia and the likelihood that it will become irreversible increase with the duration of antipsychotic treatment and periodically during long-term treatment.

**Falls**: There were no reports of falls for CAPLYTA or placebo in the uncontrolled open-label trial.

**Seizures**: Like other antipsychotic drugs, CAPLYTA may cause seizures. The risk is greatest in patients with a history of seizures.

**Orthostatic Hypotension**: Orthostatic vital signs should be monitored in elderly patients, in patients with a history of orthostatic hypotension, and in patients receiving concomitant medications that may exacerbate orthostatic hypotension.

**Hyperosmolar coma or death**: There have been reports of hyperosmolar coma or death, has been reported in patients treated with antipsychotics. There have been reports of hyperosmolar coma or death, has been reported in patients treated with antipsychotics. There have been reports of hyperosmolar coma or death, has been reported in patients treated with antipsychotics. There have been reports of hyperosmolar coma or death, has been reported in patients treated with antipsychotics. There have been reports of hyperosmolar coma or death, has been reported in patients treated with antipsychotics.

**Liver Function Tests**: Increases Compared to Placebo

**Clinical Trials Experience**: Increases in liver function tests have been observed in up to 2.1% of patients treated with CAPLYTA. Increases in liver function tests have been observed in up to 2.1% of patients treated with CAPLYTA. Increases in liver function tests have been observed in up to 2.1% of patients treated with CAPLYTA. Increases in liver function tests have been observed in up to 2.1% of patients treated with CAPLYTA. Increases in liver function tests have been observed in up to 2.1% of patients treated with CAPLYTA.

**Use in Specific Populations**

**Pregnancy**: Pregnancy Registry - There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to atypical antipsychotics, including CAPLYTA, during pregnancy. Healthcare providers are encouraged to register patients by contacting the National Registry for Atypical Antipsychotics at 1-866-961-2388 or online at www.womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/.

**Neonates** Neonates exposed to antipsychotic drugs during the third trimester are at risk for extrapyramidal and/or withdrawal symptoms following delivery (see Clinical Considerations). Available data from case reports on CAPLYTA use in pregnant women are insufficient to establish any drug-associated risks for birth defects, miscarriage, or adverse maternal or fetal outcomes. There are risks to the mother associated with untreated schizophrenia and with exposure to antipsychotics, including CAPLYTA, during pregnancy (see Clinical Considerations). In animal reproduction studies, no malformations were observed with oral administration of lumateperone to pregnant rats and rabbits during organogenesis at doses of up to 3.1 and 9.3 times, respectively, the maximum recommended human dose (MRHD) of 42 mg/day on a mg/m2 basis. When pregnant rats were administered lumateperone during the period of organogenesis through lactation, the number of perinatal deaths of pups was increased at 4.9 times the MRHD, with no adverse effects on pups at 2.4 times the MRHD (see Data).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

**Clinical Considerations - Dose-related inhibition of maternal and/or embryonic/fetal risk**: There is risk to the mother from untreated schizophrenia, including increased risk of relapse, hospitalization, and suicide. Schizophrenia is associated with increased adverse perinatal outcomes, including preterm birth. It is not known if this is a direct result of the illness or other confounding factors.

Fetal/neonatal adverse reactions - Extrapyramidal and/or withdrawal symptoms, including agitation, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder have been reported in neonates who were exposed to antipsychotics. Extrapyramidal and/or withdrawal sympotms may occur in neonates exposed to antipsychotics during the third trimester of pregnancy. These symptoms have varied in severity. Monitor neonates for extrapyramidal and/or withdrawal symptoms and manage symptoms appropriately. Some neonates recovered within hours or days without specific treatment; others required hospitalization.

Data - Animal Data - Pregnant rats were treated with oral doses of 3.5, 10.5, 21, and 63 mg/kg/day lumateperone (0.8, 2.4, 4.9, and 14.6 times the MRHD on a mg/m2 basis) during the period of organogenesis. No malformations were observed with lumateperone at doses up to 2.4 times the MRHD. Findings of decreased body weight were observed in fetuses at 4.9 and 14.6 times the MRHD. Findings of incomplete ossification and increased incidences of visceral and skeletal variations were recorded in fetuses at 4.9 to 14.6 times the MRHD, a dose that induced maternal toxicity.

Pregnant rabbits were treated with oral doses of 2.1, 7.1, and 21 mg/kg/day lumateperone (1.0, 3.2, and 9.7 times the MRHD on a mg/m2 basis) during the period of organogenesis. Lumateperone did not cause adverse developmental effects at doses up to 4.9 times the MRHD.

In a study in which pregnant rats were administered oral doses of 3.5, 10.5, and 21 mg/kg/day lumateperone (0.8, 2.4, and 4.9 times the MRHD on a mg/m2 basis) during the period of organogenesis and through lactation, the number of live-born pups was decreased at 2.4 and 4.9 times the MRHD, and early postnatal deaths increased at a dose 4.9 times the MRHD. Impaired nursing and decreased body weight gain in pups were observed at 4.9 times, but not at 2.4 times, the MRHD.

Pregnant rats were treated with a human metabolic equivalent of lumateperone (reduced ketone metabolite) at oral doses of 15, 50, and 100 mg/kg/day (1.2, 19, and 37 times the exposure to this metabolite at the MRHD of lumateperone based on AUC plasma exposure) during the period of organogenesis. This metabolite did not cause adverse developmental effects at doses up to 2.6 times the exposure at the MRHD of lumateperone; however, it caused an increase in visceral malformations (cleft palate) at 27 times and skeletal malformations at 19 times the exposure at the MRHD of lumateperone, a dose that induced maternal toxicity.

**Lactation**: Risk Summary - There are no available data on the presence of lumateperone or its metabolites in human milk or animal milk, the effects on the breastfed infant, or the effects on milk production. Toxicity in animals has been linked to the formation of airborne metabolites of lumateperone. Although airborne metabolites were not present in (adult) humans at quantifiable levels, it is unknown whether infants exposed to lumateperone will exhibit comparable lumateperone metabolism and elimination pathways as adults. In addition, there are currently no data on the short-term or long-term effects of maternal exposure to lumateperone (systemic or airborne movements) in breastfed infants exposed to antipsychotics. Based on findings of toxicity in animal studies and the potential for serious adverse reactions in the breastfed infant, breastfeeding is not recommended for mothers treated with CAPLYTA.

**Females and Males of Reproductive Potential**: Infertility - Based on findings from animal studies, lumateperone may impair male and female fertility.

**Geriatric Use**: Safety and effectiveness of CAPLYTA have not been established in pediatric patients. Antipsychotics increased the risk of suicidal thoughts and behaviors in pediatric patients.

**Antipsychotics**: Antipsychotic drugs increase the risk of death in elderly patients with dementia-related psychosis.

**Hepatic Impairment** - Patients with moderate (Child-Pugh class B) and severe (Child-Pugh class C) hepatic impairment generally had higher exposure to lumateperone than patients with normal hepatic function; therefore, a dosage reduction of CAPLYTA is recommended in patients with moderate or severe hepaptic impairment.

No dosage adjustment is recommended for patients with mild hepatic impairment (Child-Pugh class A).

**OVERDOSAGE**

No specific antidotes for CAPLYTA are known. In managing overdose, provide supportive care, including treatment of the underlying causes and monitoring for the possibility of multiple drug involvement. In case of overdose, consult a certified Poison Control Center (1-800-222-1222 or www.poison.org).

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Margie Balfour, MD, PhD

One of the most significant health care disparities involves the way our society addresses behavioral health emergencies. Although a 911 call for chest pain results in the dispatching of an ambulance with trained emergency medical technicians, a call for suicidal ideation often brings a response from armed law enforcement. Because police are the default first responders, individuals in behavioral health crisis account for more than 2 million jail bookings and a quarter of police shootings every year. These disparities are amplified for people of color, with Black Americans 2.6 times more likely than non-Hispanic white individuals to be killed by police—and this risk is nearly 10-fold for Black Americans with mental illness. 1

The inequity continues at the emergency department (ED), where the patient with chest pain receives rapid assessment, treatment, and, if needed, admission to an inpatient bed, usually in the same hospital. The individual with the behavioral health emergency has a very different experience. Most EDs and hospitals lack the capability to provide psychiatric assessment and treatment. Instead, an individual can “board” for hours, even days, awaiting transfer to an outside facility for inpatient psychiatric admission. In addition to the poor experience for the individual in crisis, this creates significant operational and financial burdens on the health care system. We can and should do better.

Fortunately, catalysts have converged to create the right conditions for transformative change:

- The COVID-19 pandemic and associated stresses have elevated awareness of the importance of behavioral health care. Relief packages and other pending legislation contain increased funding for expanded behavioral health services, infrastructure, and workforce, often with broad bipartisan support.

- The new 988 mental health crisis line went live in July 2022. Although the initial soft launch focused on improving access to suicide hotline services, 988 represents the first step in a much-needed expansion of behavioral health crisis care, just as 911 precipitated the development of emergency medical systems and trauma care.

Social justice movements have sparked a national conversation about policing reform. Most agree that law enforcement should not be the default first responders to behavioral health emergencies, and community leaders are looking to build or partner with crisis services as an alternative to police involvement.

To make the most of this pivotal moment, we need a clear vision for behavioral health crisis systems and a pathway to get there. This was our intention in creating the Roadmap to the Ideal Crisis System: Essential Elements, Measurable Standards and Best Practices for Behavioral Health Crisis Response. Written by the Group for the Advancement of Psychiatry Committee on Psychiatry and the Community, and published by the National Council for Mental Wellbeing, the report makes several bold statements in its vision, beginning with the use of the word “ideal.” For too long, we have settled for a patchwork of poorly coordinated, inadequately resourced services that do not meet the needs of individuals and families struggling with behavioral health emergencies. The Roadmap posits that a behavioral health crisis system is an essential community service from which we should expect the same quality and consistency as medical emergency response. It should be able to serve everyone regardless of payer, age, or acuity, including those with co-occurring substance use disorders, development disabilities, and involuntary legal status. Furthermore, a crisis system is more than a single program or collection of services—it is a coordinated system with a governance and accountability structure that ensures needs are met effectively and efficiently.

To achieve this ideal, the Roadmap describes 3 interacting design elements along with measurable indicators for each (Figure). These elements provide the structure for the major sections of the report: (1) accountability and finance, (2) service continuum and capacities, and (3) clinical best practices.

At all points along the continuum, easy access for law enforcement facilitates connection to treatment instead of arrest.
The report also outlines steps community leaders and advocates can take to begin planning, implementation, and continuous improvement. This framework complements the other reports that focus on defining core elements of the service continuum (eg, the Substance Abuse and Mental Health Services Administration’s [SAMHSA] Best Practice Toolkit and its “someone to call, someone to respond, somewhere to go” rubric).

The Arizona crisis system demonstrates how the concepts outlined in the Roadmap can be put into practice in real-world settings. In the accompanying graphic, based on the crisis system in Tucson, a robust continuum of programs and services work together as a coordinated system. Stakeholders agree on common system values such as preventing avoidable jail, ED, and hospital use by providing care in the least restrictive setting that can safely meet the needs of an individual experiencing a crisis. The crisis continuum is composed of an array of services organized along a continuum of intensity, restrictiveness, and cost (Figure 2). At all points along the continuum, easy access for law enforcement (eg, crisis line staff colocated with 911, crisis facilities with quick police turnaround times and “no wrong door” policies) facilitates connection to treatment instead of arrest.

Governance and accountability are key to ensuring that crisis services operate as an organized, coordinated system. In the Arizona model, the Regional Behavioral Health Authority (RBHA) serves as the “accountable entity” via its role as the single payer and regulator for the crisis system. The RBHA contracts with multiple service providers to create the crisis continuum and sets expectations for system performance that are aligned with overarching system goals. Contracts and culture confer a “preferred customer” status to law enforcement to law enforcement so that, for example, response time targets for mobile crisis are faster for calls involving law enforcement. To maximize the impact of all funding streams, the RBHA is financed via braided funding from a variety of sources (eg, Medicaid, SAMHSA block grants, state and local funds) and accountable to the state for clinical and fiscal outcomes. Because less restrictive community-based care settings tend to be less costly, the result is a sustainable system that is a worthwhile investment from a clinical and fiscal standpoint.

The next several years pose a golden opportunity for determining the future of behavioral health crisis care in the United States. This is the perfect time for psychiatrists and other clinical leaders to get involved and make a difference.

Here are some suggestions:

- Read the Roadmap to the Ideal Crisis System report.
- All states have received federal grant funds for crisis system planning. Find out who is leading these efforts in your state and/ or local community and offer to help provide stakeholder feedback and representation.
- Stay abreast of federal and local legislation via professional societies or advocacy organizations like the National Alliance on Mental Illness’ #ReimagineCrisis campaign. Key issues include increased crisis funding via the SAMHSA block grants; parity coverage by private health plans for behavioral health crisis services commiserate with that of medical emergencies; and workforce development incentives such as loan repayment for those working in crisis care sites.

These are exciting times for crisis care. Carpe diem.

Dr Balfour is the chief of quality and clinical innovation at Connections Health Solutions and an associate professor of psychiatry at the University of Arizona. She is a coauthor of the report, Roadmap to the Ideal Crisis System: Essential Elements, Measurable Standards and Best Practices for Behavioral Health Crisis Response.

![Figure 2. Alignment of Crisis Services Toward Common Goals](image-url)

Alignment of crisis services toward common goals

**Figure 2. Alignment of Crisis Services Toward Common Goals**

- **Easy access for police = Connection to care instead of arrest (Sequential Intercept Model 0 and 1)**
- **Person in Crisis**
- **Crisis Line 988**
- **Mobile Crisis**
- **Acute Crisis Facilities**
  - **80% resolved on the phone**
  - **70% resolved in the field**
  - **60-70% discharged to the community**
- **Community & Residential Care**
  - **Post-crisis wraparound**
  - **85% remain stable in community-based care > 45 days**
- **Result: Decreased Use of Jail, ER, hospital**

Services are easily accessible with a no-wrong door culture across the continuum, e.g., walk-ins at crisis facilities, police or mobile drops-offs to crisis residential, etc.

References

The Gut Microbiome and Beyond: Dietary Influences in ADHD

Jun Park; Noel Amaladoss, MD

Patients, clinicians, and researchers have shown increasing interest in the potential role of diet and supplements in the treatment of attention-deficit/hyperactivity disorder (ADHD) symptoms. Because diet is a lifestyle change rather than a medication, it is an important treatment approach to consider. Research shows that at least 10% to 30% of children with ADHD are nonresponsive to—or experience adverse effects from—ADHD medications.1 Thus, a dietary approach to ADHD can be complementary to a conventional pharmacological strategy, giving patients and their families more options for personalized treatment plans. This article will examine current research about diet and ADHD, review important potential mechanisms (including the roles of the immune system, gut microbiome, and toxic heavy metals), and discuss promising new avenues for treatment.

Elimination Diets

Elimination diets have been developed for ADHD since the 1970s, beginning with the Feingold diet, which was based on a hypothesis that a diet without natural salicylates and artificial food coloring could improve symptoms in hyperactive children.2 Of more recent research interest has been the oligoantigenic diet, a strategy that removes major common food allergens including wheat, dairy, and gluten and restricting the diet to a few hypoallergenic foods.3 Randomized controlled trials (RCTs) have shown the effectiveness of the oligoantigenic diet in patients with ADHD. A 2012 meta-analysis across 6 trials including 195 patients reported an effect size of 0.29, and it was concluded that about one-third of the children with ADHD showed an excellent (greater than 40% symptom reduction) response.4 It is not clear whether there are biomarkers or other indicators to predict whether a patient belongs to a subset that responds more favorably to the oligoantigenic diet.5

The mechanism behind the efficacy of the oligoantigenic diet remains under investigation. Patients with ADHD are more likely to develop allergies, and vice versa, which has led investigators to study potential immunoglobulin E (IgE) responses to foods in children with ADHD.6 So far, there has been no convincing evidence to suggest an IgE-mediated mechanism; for example, there were no differences found in allergen skin-prick testing results between children with ADHD and control patients.6 Potential mechanisms involving serum immunoglobulin G (IgG) levels have been investigated, but no associations have been found between IgG levels and ADHD symptom remission.3

Gut Microbiome

There has been increasing evidence suggesting that the gut microbiome plays an important role in the gut-brain axis, and that dysbiosis may contribute to several neurodevelopmental disorders including autism spectrum disorder (ASD) and ADHD.7 The gut microbiome has multiple ways it can influence brain development and functioning via its direct connections with the vagus nerve and its interactions with the immune system, as well as by directly altering the level of neurotransmitters like serotonin (5-hydroxytryptamine) and dopamine. Changes in composition of the gut microbiome, therefore, can affect neurodevelopment and functioning.3

For instance, investigators studied the profile of gut microbiota in patients with ADHD and found that they had a 12.7% to 20.5% increased Bifidobacterium genus. It was also found that an increased proportion of Bifidobacterium could predict the function of dopamine precursor synthesis and was associated with diminished neural reward anticipation on functional MRI.8 Another potential indication of the involvement of the gut microbiome in ADHD comes from research on probiotics. A recent RCT examined the role of the probiotic strain Lactobacillus GG (LGG) in patients with ADHD and found that children and adolescents who received LGG supplementation reported better health-related quality of life compared with peers who received the placebo. However, there were no significant reported differences in the ADHD symptom ratings provided by parents and teachers.9

Heavy Metals

Exposure to heavy metals is one of the environmental factors most implicated in ADHD.10 Many heavy metals are known developmental neurotoxicants including lead, mercury, arsenic, manganese, and selenium. In utero, these metals are transferred from mother to fetus via the placenta; with additional exposure during infancy and adolescence, children can develop neurodevelopmental deficits seen in disorders such as ADHD and ASD.11 The developing human brain is particularly vulnerable to toxic chemicals; levels of exposure that would have little or no adverse effects in an adult can result in permanent brain injury in an infant.12

Several studies corroborate the connection between ADHD and heavy metals. A 2020 study in Guangzhou, China, for example, reported that children with ADHD presented with higher urine concentrations of chromium, manganese, cobalt, nickel, copper, molybdenum, tin, barium, and lead, whereas a study of children in a city in Chile with known heavy metal contamination found positive associations between urinary arsenic and blood lead levels and the diagnosis of ADHD.13 Furthermore, the presence of lead in children’s deciduous teeth was found to be positively

"The Gut Microbiome and Beyond: Dietary Influences in ADHD" JUN PARK, NOEL AMALADOSS, MD
associated with hyperactivity or impulsivity, as well as inattention and oppositional or defiant disorder.15 The most common therapeutic strategy for heavy metal toxicity is chelation therapy. However, chelators have safety and efficacy concerns, with risks of renal toxicity, unwanted gastrointestinal adverse effects, and a lack of specificity causing the depletion of essential metals such as zinc and iron.14 Dietary strategies against heavy metal toxicity are an effective alternative, because they can easily be added to patients’ routines with minimal adverse effects.

A variety of essential metals, vitamins, nutrients from foods, and probiotics can lead to decreased heavy metal toxicity. Zinc is one of the most-studied essential metals for the alleviation of heavy metal toxicity. It upregulates the synthesis of metallothionein, which detoxifies heavy metals by binding to it. It also exerts antioxidant effects through its role as a cofactor of the antioxidant enzyme copper-zinc superoxide dismutase, alleviating the oxidative stress caused by heavy metals.15 Ascorbic acid (vitamin C) has been widely shown to exert antioxidant effects by scavenging free radicals and reducing lipid peroxidation. It also has been reported to act as a chelating agent of lead, with a potency similar to that of a known synthetic chelator.16

In addition to being important dietary sources of essential metals and vitamins, many vegetables, fruits, and other edible plants provide additional nutritional mechanisms to protect against the toxic effect of heavy metals. For example, garlic (Allium sativum) has been shown to alleviate lead-induced neural, hepatic, and renal toxicity in rats via the antioxidant properties provided by its organosulfur compounds, the direct chelating property of sulfur-containing amino acids, and the prevention of cadmium and lead absorption.17 Tomatoes are also well known for their antioxidant properties and have been reported to produce metal-chelating properties. For instance, consumption of tomato has been shown to significantly reduce the accumulation of heavy metals (cadmium, lead, and mercury) in the livers of rats.18 In addition, berries, onions, grapes, algae such as Spirulina and Chlorella, and certain probiotic strains have shown beneficial effects against heavy metal toxicity, as well as providing other essential nutrients and vitamins.19

The composition of diets may have an important effect on heavy metal accumulation and toxicity as well: Mice that were fed a high-fat diet were shown to accumulate greater levels of heavy metals in the liver and kidneys and experienced more severe functional damage in these organs than normal-diet mice, possibly due to alterations in the microbiome.19 Given these findings, a novel direction for ADHD research could include the study of diets that are low in fat and include foods and supplements with known effects against heavy metal toxicity. This could be compared against or used in combination with current oligoantigenic/low-foods diet strategies.

Supplementation Recommendations Various studies have examined the role of supplements in the amelioration of ADHD symptoms, including polyunsaturated fatty acids (PUFAs), single micronutrients such as zinc and cholecystokinin (vitamin D), micronutrient mixes, herbal supplements, and probiotics.

Rosí et al reviewed 42 RCTs that included various of the aforementioned supplementation categories and found that most studies reported beneficial effects in a wide array of treatment outcome measures. For instance, studies looking at PUFA supplementation alone found significant improvements in attention, psychosocial functioning, emotional problems, behavior as reported by parents and teachers, and working memory.10 Furthermore, it appeared that a supplementation approach was valid in combination with pharmacological treatment, as demonstrated by positive results of methylphenidate in combination with PUFAs, peptides or amino acid derivatives, zinc, vitamin D, vitamin A and magnesium, and sweet almond syrup.

However, because many of the studies had heterogeneous trial durations, methodologies, and outcome measures, the authors reported that it was not possible to carry out a meta-analysis, which would provide more systematic evidence for the effectiveness of supplements.

Conclusion

The Western dietary pattern—heavily processed and rich in saturated fat, salt, and sugars—has been shown to be associated with ADHD diagnosis, even after adjusting for multiple confounding factors.20 For patients and families on a standard Western diet, it would be sensible to make adjustments not only to alleviate ADHD symptoms but also to decrease the risk of common associated comorbidities such as obesity, diabetes, cardiovascular disease, and various cancers (Figure).21 More research is required to better understand the efficacy and underlying mechanisms of dietary strategies for ADHD. This article provides a review of currently studied as well as emerging dietary recommendations for treatment of ADHD, with the hope of providing a greater array of personalized, effective treatment options for patients with ADHD and their families.

Mr Park is an MD candidate at Michael G. DeGroote School of Medicine in Hamilton, Ontario, Canada. Dr Amaladoss is an assistant professor clinical in the Department of Psychiatry and Behavioural Neurosciences of McMaster University in Hamilton, Ontario, Canada, and a consultant psychiatrist at the Advanced Mind Clinic ADHD and Autism Centre and a a PsiAlic Times Advisory Board Member.

References

FIGURE. Key Takeaways
- A Western dietary pattern is associated with ADHD diagnosis even after adjusting for confounding factors.
- Potential causes of ADHD which dietary interventions can help with include:
  - Food allergens (eliminating common food allergens including wheat, dairy, and gluten).
  - Gut microbiome profile (use of probiotics, prebiotic rich diet)
  - Heavy metal neurotoxicity (consumption of fruits, vegetables and supplements which have proven chelating effects, as well as shifting to a lower fat intake dietary pattern)
- A novel research direction: a trial of dietary interventions including aforementioned recommendations, and comparing against therapeutic oligoantigenic diets.
The Need for Novel Treatments for Bipolar Depression

Lyons Hardy, MS, PMHNP-RN; and Brian McCarthy, MS, PMHNP-RN

Bipolar depression is a condition that proves difficult to treat for many patients. When patients with bipolar disorder (BD) go through a depressive episode, medication adjustment is often the first intervention that clinicians consider. Evidence for standard pharmacologic treatments for bipolar depression shows the strongest support for several dopamine-blocking agents, as well as for lithium and lamotrigine (Lamictal). Recently published treatment guidelines are reflective of this evidence. Pharmaceutical industry support for research on dopamine-blocking medications has contributed to their dominance in the marketplace. Older generic medications are less likely to be included in research trials and thus may not be adopted widely due to a perceived or real lack of evidence.

A number of novel pharmacologic treatments have been studied for bipolar depression, and clinicians will be well served by becoming familiar with them. When standard treatments fail or cause intolerable adverse effects, having another set of options in your arsenal can be invaluable. In addition, utilizing nonpharmacologic treatments that have been shown to be effective for managing bipolar depression is another important component of a comprehensive treatment plan.

CASE STUDY “Sam” is a nonbinary person assigned female at birth, aged 22 years, who is diagnosed with BD II. They have a personal history of depressive episodes, anxiety symptoms, and hypomanic symptoms, as well as a strong family history of BD. They were originally diagnosed with major depressive disorder and generalized anxiety disorder in high school and, at that time, tried escitalopram, bupropion, and gabapentin. After the initial diagnosis of BD at age 21 years, Sam tried lamotrigine with poor results. They were started on lithium, which kept their mood stable for about a year until they began to experience a depressive episode that included hypersomnia, depressed mood, poor energy and motivation, poor appetite, and suicidal thoughts. Sam’s lithium level was 0.8 mmol/L, and they did not tolerate higher doses due to adverse effects. They tried several dopamine-blocking medications but were unable to tolerate any of them due to adverse effects, primarily sedation. Sam also tried a serotonin reuptake inhibitor in conjunction with lithium without effect on mood.

Bipolar Depression Treatment Guidelines

Standard pharmacologic treatments for bipolar depression are covered in various published treatment guidelines (Table 1). There are currently 4 guidelines that are less than 10 years old, and they include recommendations for treating acute bipolar depression. The organizations that have released these guidelines are the British Association for Psychopharmacology, the Canadian Network for Mood and Anxiety Treatments and the International Society for Bipolar Disorders (CANMAT/ISBD), the National Institute for Health and Care Excellence, and the Royal Australian and New Zealand College of Psychiatrists. Each of these guidelines emphasizes the importance of nonpharmacologic interventions such as psychotherapy, family engagement, and addressing substance misuse. Although these are important interventions, a detailed discussion of them is beyond the scope of this article.

The guidelines also include recommendations for pharmacologic treatments for acute bipolar depression. The CANMAT/ISBD guidelines include many of the novel treatments
(which will be discussed here and in Part 2) as third-line recommendations. Guidelines also promote the engagement of the patient/service user in the treatment-planning process, and they highlight the importance of selecting interventions that are agreeable and likely to be followed. Clinicians may have the best of intentions in selecting treatments that are reflected in treatment guidelines, but if the patient is not on board due to concerns about adverse effects or difficulty achieving the recommendation (eg, exercise is not possible due to physical limitations, patient is unable to access psychotherapy due to lack of insurance coverage, etc), the treatment plan needs to go in a different direction.

**Using Novel Treatment Protocols**

If first-line, FDA-approved treatments have been trialed without success, it becomes necessary to use treatments that lack official FDA approval. Whatever is chosen, treatment options should be evidence based. All of the medications and interventions discussed have varying degrees of evidence. Clinicians should understand what the levels of evidence signify and should have reasonable expectations for the effect size of the drug or therapeutic intervention used.

Nassir Ghaemi, MD, MPH, an expert in this field, provides a concise and useful overview of evidence levels; he ranks them as levels 1 through 5, with the strongest evidence at level 1 and the weakest at level 5. Level 1 includes blinded randomized controlled trials (RCTs); level 2, open-label RCTs; level 3, large observational studies; level 4, small observational studies; and level 5, expert opinions and case studies. However, as Ghaemi has noted, level 4 or 5 evidence—although weaker—is not necessarily without value. Rather, the designation simply means that the evidence is not as strong. In a perfect world, treatment choices would be guided by evidence at levels 1 and 2. In the real world, however, conducting blinded RCTs on every treatment option is not always feasible or possible.

When patients struggle for relief from debilitating symptoms, it is often necessary to push forward with options that have a weaker evidence base. As clinicians progress down the levels of evidence, they should have realistic expectations of outcomes. When using third- and fourth-line treatments, the expected result may only be some degree of symptom relief and not complete remission. Fortunately, when patients present with severe symptoms, even a slight degree of improvement is usually welcome and acceptable to the patient. Additionally, patients may be interested in trying non-pharmacologic approaches as well as different pharmacologic options. The treatments to be discussed in this article have been listed according to their levels of evidence in Table 2. Part 2 will explore the use of these treatments, which address different targets based on a current

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**TABLE 1. Available Treatment Guidelines**

<table>
<thead>
<tr>
<th>Organization</th>
<th>Recommended pharmacologic treatments</th>
<th>Recommended nonpharmacologic treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>British Association for Psychopharmacology (2016)</td>
<td>• Quetiapine • Olanzapine/fluoxetine combo (OFC) • Lurasidone</td>
<td>• Antidepressants in combination with anti-manic agent • Lamotrigine • Lithium</td>
</tr>
<tr>
<td>Canadian Network for Mood and Anxiety Treatments/International Society for Bipolar Disorders (2018)</td>
<td>First line: Quetiapine • Lurasidone + VPA/lithium • Lithium • Lamotrigine • Lamotrigine adjunct Second line: VPA • SRIs/bupropion adjunct • Cariprazine • OFC</td>
<td>Third line: Aripiprazole adjunct • Armadafinil adjunct • Asenapine adjunct • Carbamazepine • EPA adjunct • Ketamine/HV adjunct • Levotyroxine adjunct • Modafinil adjunct • NAC adjunct • Olanzapine • Pramipexole adjunct • SNRI/MAOI</td>
</tr>
<tr>
<td>National Institute for Health and Care Excellence (updated 2020)</td>
<td>• OFC • Quetiapine • Olanzapine monotherapy, if preferred by patient</td>
<td>• Lamotrigine, if preferred by patient</td>
</tr>
<tr>
<td>Royal Australian and New Zealand College of Psychiatrists (2020)</td>
<td>Monotherapy First line: Lithium Second line: Lamotrigine Monotherapy Third line: Valproate Fourth line:quetiapine Fifth line: lurasidone Sixth line: cariprazine Or consider combination therapy Dyads are preferred over triads Mood-stabilizing agents (MSAs) are preferred over second-generation antipsychotics (SGAs) and/or antidepressants • Two MSAs • MSA + SGA • MSA + antidepressant • SGA + antidepressant • Two SSAs + antidepressant ECT</td>
<td>Further options • Carbamazepine • Olanzapine Adjuvant • Asenapine • Armadafinil • Levotyroxine</td>
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September 2022

CME

understanding of the pathophysiology of psychiatric illness.

Inflammation and the Microbiome

A growing body of research supports the role of inflammation in the pathology of BD as well as in unipolar depression. The results of numerous studies have shown elevated proinflammatory cytokine levels in patients with BD. C-reactive protein was found to be significantly elevated in patients with BD during mania and more moderately so in depressive episodes. These findings can direct clinicians toward new treatment paths for patients who struggle with difficult-to-treat bipolar depression. Choosing treatments that target inflammation may improve the efficacy of current drug regimens and may also boost patients’ overall health. Many of the interventions discussed in this article are thought to target inflammation. These include probiotics, exercise, sleep, diet, and actual anti-inflammatory agents such as celecoxib.

Within the context of the inflammatory hypothesis are the roles of the microbiome and the gut-brain axis, which comprises several somatic components, including the gut microbiome, enteric nervous system, vagus nerve, neuroendocrine system, and central nervous system. The relationship between inflammation and the microbiome is currently not well understood, but it is known that the gut microbiome impacts immune system functioning through its relationship with cytokine modulation. In addition, gut microbiota modulate the production of neurotransmitters, and have been shown to be altered in individuals with BD, although findings have been mixed. External factors that may influence the biodiversity of the gut microbiome include diet, alcohol and other substances, medication, environment, genetics, and mode of birth (vaginal versus Cesarean). Evidence points toward a possible causal relationship between gut-brain axis alterations and the development of BD and other psychiatric disorders, mediated by epigenetic changes. Current knowledge of the relationship among the gut-brain axis, immune system activity, inflammation, and psychiatric symptoms has not yet yielded strong evidence for specific treatment interventions, but emerging evidence provides some support for the use of modalities such as anti-inflammatory diets and medications.

Clinical Decision-Making With Novel Approaches

When standard treatments have not worked, an important first step is to rework the diagnosis using evidence-based assessment tools. Some indispensable tools include the Mini International Neuropsychiatric Interview (MINI) and the Harvard Bipolarity Index (HBI). The MINI has been validated and is often more accurate than clinician opinion alone. The HBI is also key in helping clinicians to refine a diagnosis and to distinguish between BD and other psychiatric conditions.

The HBI considers 5 clinical domains: signs and symptoms, age of onset, course of illness, response to treatment, and family history. A score of 50 or more highly suggests a BD diagnosis. Additionally, screening for the presence of trauma may be helpful, as a comorbid trauma diagnosis makes treating most psychiatric conditions more difficult. A tool such as the Adverse Childhood Experiences Questionnaire can also be useful, although some critics say that this tool may not be substantive enough to fully assess the impacts of childhood trauma. Use of the Clinician-Administered PTSD [posttraumatic stress disorder] Scale for DSM-5 is also advised. All of these tools are relatively easy to use and will increase the likelihood of an accurate diagnosis.

After confirming or altering the diagnosis, clinicians can then move on to selecting appropriate treatment options. If a diagnosis of bipolar depression is confirmed, and standard treatments have been unsuccessful, clinicians can begin to explore the treatments that will be discussed further in Part 2. Although using treatments that are not FDA approved may be a new experience for some clinicians, the evidence hierarchy can guide clinical decision-making. There is no evidence that trying more and more medications with the same mechanism of action is likely to be effective. Indeed, selecting pharmacologic interventions with different mechanisms of action that have evidence of efficacy in the treatment of bipolar depression is a sensible strategy. Patients may require a combined strategy of nonpharmacologic and pharmacologic interventions. Because many of the nonpharmacologic interventions are conducive to overall health and well-being and have minimal to no adverse effects, there is little harm in trying them alongside pharmacologic interventions.

Evaluating patient-specific factors is also important when selecting treatments. Clinicians should already be familiar with this process when using standard FDA-approved medications. For example, if a patient has type 2 diabetes and obesity, most clinicians would be less likely to select a dopamine-blocking medication with a high risk for metabolic adverse effects. Similarly, for patients who have comorbid inflammatory conditions, the use of anti-inflammatory agents may be a wise choice. Patients who have accompanying neurocognitive symptoms may benefit from a dopamine agonist medication. For patients with limited resources, light box therapy may not be attainable and would not be a reasonable recommendation. In that case, a recommendation to sit outdoors for 30 minutes every morning would be more realistic. One potential benefit of using older generic medications is that they may be more accessible than newer brand-name drugs.

Tailoring treatment selections to the patient’s individual needs and preferences may increase the likelihood of success.

<table>
<thead>
<tr>
<th>TABLE 2. Evidence Levels</th>
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<tr>
<td><strong>LEVEL 1</strong> Double blind RCTs</td>
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<tr>
<td><strong>LEVEL 2</strong> Open-label RCTs</td>
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<tr>
<td><strong>LEVEL 3</strong> Large observational studies</td>
</tr>
<tr>
<td><strong>LEVEL 4</strong> Small observational studies</td>
</tr>
<tr>
<td><strong>LEVEL 5</strong> Expert opinions and case studies</td>
</tr>
</tbody>
</table>

Specific treatment interventions, but emerging evidence provides some support for the use of modalities such as anti-inflammatory diets and medications.
About 3 weeks later, Sam began to notice improvement in motivation and energy, appetite, sleep patterns, and suicidal thoughts. Their depressed mood persisted, however, and Sam’s therapist noted it was likely related to situational factors and past trauma. Sam experiences a great deal of family stress associated with their mother and grief related to their father’s death about 3 weeks prior. Sam and their therapist continued to work through these issues, and Sam’s mood slowly improved over the next several months.

NP Hardy is a psychiatric mental health nurse practitioner and clinical assistant professor at the Virginia Commonwealth University School of Nursing in Richmond, VA. Mr. McCarthy is a psychiatric mental health nurse practitioner at the Mood Treatment Center in Winston-Salem, NC.

References
Psychiatrists: We’re recruiting Medical Directors

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

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

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

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

Salary and Benefits

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

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

Don’t Miss the Latest Updates in Child and Adolescent Psychiatry!

Visit www.aacap.org/AnnualMeeting-2022 for complete details!
Full-time or part-time Psychiatrists

Cambridge Health Alliance (CHA)

Outpatient Psychiatrist Opportunities

Cambridge Health Alliance, a well-respected, nationally recognized and award-winning public healthcare system is seeking Full-time or Part-time Psychiatrists to join our Adult Outpatient Psychiatry service. The Department of Psychiatry is recognized as a leader in patient care, teaching and research. As a leader in mental health for more than 20 years, CHA’s psychiatry teams provide compassionate care to our diverse patient population. CHA is comprised of an established network of ambulatory clinics, an urgent care site and two full service hospitals based in Cambridge, Somerville, and Boston’s metro-north communities.

• Full-time or part-time opportunities available in Revere, Everett, and Cambridge areas
• Work with a multidisciplinary team serving the local community and providing high quality care to our underserved and diverse patient population
• Fully integrated electronic medical record (EPIC) is utilized
• Our Psychiatry service is comprised of award-winning training programs in Adult and Child Psychiatry, Geriatric Psychiatry and Psychosomatic Medicine.
• CHA is a teaching affiliate of Harvard Medical School and academic appointments are available commensurate with medical school criteria

CHA offers competitive compensation and a comprehensive benefits package including health and dental insurance, 403b retirement accounts with matching, generous PTO, CME allotment (time and dollars) and more.

Please send CV’s via email to Melissa Kelley at ProviderRecruitment@challiance.org.

In keeping with federal, state and local laws, Cambridge Health Alliance (CHA) policy forbids employees and associates to discriminate against anyone based on race, religion, color, gender, age, marital status, national origin, sexual orientation, relationship identity or relationship structure, gender identity or expression, veteran status, disability or any other characteristic protected by law. We are committed to establishing and maintaining a workplace free of discrimination. We are fully committed to equal employment opportunity.
Arizona

MEDICAL DIRECTOR
BRAND NEW PSYCHIATRY UNIT IN YUMA, AZ.

Be in on the beginning of a new Psychiatry Service, helping to mold it and develop it!

Seeking a Medical Director on a new inpatient Psychiatry service at the Yuma Regional Medical Center, Yuma, AZ. The Psychiatry service will start out as 24 Adult beds and will expand to include a Geriatric Psychiatry Unit and a Detox Unit. Outpatient services are already in place. Position includes part-time admin responsibilities and patient care. YRMC is a 406-bed facility and is the only full-service Regional Medical Center, Yuma, AZ. The Psychiatrist position is available as well.

Outpatient services are already in place. Please consider this exciting opportunity to be in on the start-up of a brand new Psychiatry service from the ground up; and join YRMC’s outstanding medical staff, which is comprised of more than 500 providers in over 40 specialties. Staff Psychiatrist position is available as well. Please send CV to Terry Good at terry.good@horizonhealth.com; or call 1-804-684-5241. EOE

California

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 Mexico. San Diego State University maintains a satellite campus in Calexico, and there are several private and public universities located in Imperial. 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-1B 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: Marcy Sesma (442) 265-1605 marcysesma@co.imperial.ca.us

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 BHSadmin@sjcbhs.org. EOE

Georgia

PSYCHIATRIST JOB OPENING
Southeastern Behavioral Medicine is expanding our outpatient Psychiatry practice to Gainesville and Lake Oconee to meet Georgia’s growing mental health care needs. We have an immediate need for two psychiatrists to work with our clinical team and the founder of our practice, Dr. Thomas McCormack, who is a Clinical Professor at the UGA/ Augusta University Medical Partnership holding board certifications in Child & Adolescent, General, and Forensic Psychiatry. The fulltime positions are 100% outpatient clinical work with adults possibly children and adolescents if the candidate has particular interest or experience working with younger patients. The successful applicant will have the opportunity to serve as a clinical professor at the medical college and administer transcranial magnetic stimulation for refractory depression if desired.

Founded in Athens, Georgia as Athens Behavioral Medicine, our private practice has earned a well-deserved excellent reputation over 20 years serving patients across north Georgia. Our team utilizes a multidisciplinary bi-psycho-social-spiritual/approach, employing physicians, nurse practitioners, physician assistants, and psychotherapists to deliver outstanding mental health care.

The income opportunity and benefits package for this position are outstanding, exceeding $300,000+. Gainesville is the medical hub of northeast Georgia, and its large medical community supports the education of medical students from Augusta University (formerly the Medical College of Georgia). Located on beautiful Lake Lanier, Gainesville is a vibrant community boasting cultural and recreational activities with a modest cost of living.

Lake Oconee is home to a number of golf communities, including Reynolds Plantation and Harbor Club, as well as the upscale Ritz Carleton resort. Lake Oconee runs through three counties – Morgan, Putnam, and Greene.

Both locations are a short distance from Atlanta and Athens/University of Georgia and offer a variety of sports, night life, and cultural activities.

Interested candidates may email a cover letter along with their CV to KHerrin@athensbehavioral.com or contact our HR manager, Katie Herrin, at (706) 316-1908

New Mexico

Exciting Opportunity for Psychiatrists in the Beautiful Southwest
San Juan Health Partners in Farmington, New Mexico is recruiting one General Psychiatrist for primary inpatient care plus call and one General Psychiatrist for primary outpatient care plus call. Join a caring, community hospital in the heart of the Four Corners.

You can look forward to:
• Compensation range based on years of experience
  o Less than two years of experience $277,000
  o Two or more years of experience $310,000
• 1-3 call
• Productivity/quality bonus potential

The study of New Jersey is an Equal Opportunity Employer.
North Carolina

We Want You to Join Our Behavioral Health Team!

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

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

**Emergency Opportunity**

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

**Adult Outpatient Opportunity**

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

**Child Outpatient Opportunity**

- BE/BC Child & Adolescent providers. The current structure is for 50% outpatient Monday through Friday work schedule. We offer best in class compensation plus generous benefits including Paid Malpractice, CME Time and Allowance, Accrued Paid Time Off, 403(b) match and 457(b), Health, Dental, and other desirable benefits.

Contact Suzy Cobb, Physician Recruiter for more details at (910) 615-1889 or scob2b@capefearyvalley.com

Ohio

**HORIZON HEALTH**

**MEDICAL DIRECTOR – INPATIENT GERIATRIC PSYCHIATRY UNIT NEAR CLEVELAND**

University Hospital Lake Health Continuing Care Campus in Concord Township, OH – Seeking Psychiatrist for Medical Director position on their 20-bed inpatient Geriatric Psychiatry Unit—housed in a beautiful location, the Continuing Care Campus adjacent to the Tripoint Medical Center. Concord Township, an upscale growing area, is only 25 to 30 minutes away from downtown Cleveland. This position is a combination of part-time administration responsibilities and patient care. The hospital can offer either a full-time salaried position with benefits; or they can contract with a Psychiatrist or group in the area that wish to incorporate inpatient work into their practice. This position fits in well with someone’s private practice, rounding on patients in the morning and going to office in afternoon. Admin duties can be done while at the hospital.

Work with top-notch clinical team which includes a FT mid-level. Seeking a Psychiatrist passionate about the work that she/he does improving the lives they touch each and every day. This hospital is part of a large impressive hospital system in northern Ohio called University Hospitals serving the needs of patients through an integrated network of 23 hospitals (including 5 joint ventures), more than 50 health centers, outpatient facilities and 200 physician offices in 16 counties.

For more information, please contact Terry Good: 804-684-5241; terry.good@horizonhealth.com

Oregon

**PeaceHealth**

**Consult Liaison | Oregon**

PeaceHealth is seeking licensed Psychiatrists to join our Consult Service primarily working at PeaceHealth Riverbend Medical Center in Springfield, OR. Working with a varied, interesting & challenging group of patients. Mentor/teaching and research opportunities. ETC Services available. Build your career in a large, well-respected and established Inpatient and Outpatient Psychiatry group. PeaceHealth is a non-profit healthcare system serving the majestic Pacific Northwest.

Contact: Danny Keo, Provider Recruiter dkeo@peacehealth.org | (971) 404-6681

we’re committed to making Better Health easier. Looking for an amazing place to live, work and play?

We’re actively recruiting physicians specializing in psychiatry to join our dynamic and growing multi-specialty group with opportunities across the country. Comprised of over 4,000 physicians and healthcare professionals, our culturally diverse and world-class teams provide services to New York City Health + Hospitals (H+H), the largest public health system in the United States.

Become part of our New York-Bronx Healthcare Network, affiliated with Albert Einstein College of Medicine, and located in attractive and safe residential Bronx neighborhoods, just 20 minutes from Manhattan. Our facilities offer a full continuum of acute care inpatient and outpatient services to NYC Health + Hospitals (H+H), the largest public health system in the United States.

We're committed to making Better Health easier. Looking for an amazing place to live, work and play?

New York City Health + Hospitals/North Central Bronx

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

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

- Incentive Bonuses Available for Qualified Candidates/Providers!
- Moonlighting opportunities also available
- Academic appointments at Albert Einstein College of Medicine offered!
- Proof of Covid-19 vaccination is required prior to hire.

We offer a generous compensation package, aligned with unparalleled health benefits, opportunities for advancement, retirement plan, malpractice, sponsorship for H1 & J1 visas, and much more! We can offer unlimited J1 Waivers (instead of J1 waivers) for Psychiatrists!

For immediate consideration, please contact Joe Mastov | Physician Recruiter, at: Mastovj@pagny.org, call 646-695-3875, or apply online at: www.pagny.org
Northwell Health’s Behavioral Health Service Line strives to address the diverse mental health needs of the communities we serve by providing a continuum of accessible, high quality psychiatric and substance abuse services including emergency, crisis, inpatient, and outpatient programs for people of all ages.

WE ARE RECRUITING BE/BC PSYCHIATRISTS FOR THE FOLLOWING POSITIONS:

<table>
<thead>
<tr>
<th>Location</th>
<th>Position</th>
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<tbody>
<tr>
<td>NORTHERN WESTCHESTER HOSPITAL: Westchester, NY</td>
<td>Associate Director</td>
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<tr>
<td>COHEN CHILDREN’S MEDICAL CENTER: New Hyde Park, NY</td>
<td>Child &amp; Adolescent Psychiatrist, School Mental Health</td>
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<td></td>
<td>Psychiatrist for Emergency Department</td>
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<tr>
<td>CENTER FOR TRAUMATIC-STRESS, RESILIENCY AND RECOVERY: NYC/LI</td>
<td>Outpatient Psychiatrist</td>
</tr>
<tr>
<td>STATEN ISLAND UNIVERSITY HOSPITAL: Staten Island, NY</td>
<td>Vice Chair, Department of Psychiatry</td>
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<td>Outpatient Child &amp; Adolescent Psychiatrist</td>
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<td>Unit Chief, Inpatient Psychiatry</td>
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<td>Staff Psychiatrist, Inpatient Unit</td>
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<td>On Call Psychiatrist</td>
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<td>Addiction Psychiatrist</td>
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<tr>
<td>LONG ISLAND JEWISH MEDICAL CENTER: New Hyde Park, NY</td>
<td>Psychiatrist for Emergency Department, Part-Time</td>
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<td>LENOX HILL HOSPITAL: Manhattan, NY</td>
<td>CL Psychiatrist</td>
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<tr>
<td>ZUCKER HILLSIDE HOSPITAL: Glen Oaks, NY</td>
<td>Physician-in-Charge, Perinatal Psychiatry</td>
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<td>Adolescent Inpatient Psychiatrist</td>
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<td>Psychiatrist ETP Program, Part-Time</td>
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<td>Lead Psychiatrist, ETP Program</td>
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<td>Director, LGBTQ Psychiatry</td>
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<td></td>
<td>Outpatient Child &amp; Adolescent Psychiatrist</td>
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<tr>
<td>MATHER HOSPITAL: Port Jefferson, NY</td>
<td>Medical Director of Outpatient, Mental Health Clinic</td>
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<td>Residency Program Director</td>
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<td>Staff Psychiatrist Faculty Outpatient Clinic</td>
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<td>Weekend Outpatient Faculty Attending Psychiatrist</td>
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<td>SOUTH OAKS HOSPITAL: Amityville, NY</td>
<td>Medical Director, Outpatient Child &amp; Adolescent Psychiatry</td>
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<td>Outpatient Child &amp; Adolescent Psychiatrist</td>
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<td>Adult Inpatient Psychiatrist</td>
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<td>Child &amp; Adolescent Psychiatrist, School Based Program</td>
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<td>Child &amp; Adolescent Psychiatrist, Hospital/Outpatient</td>
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<tr>
<td>WELLBRIDGE ADDICTION TREATMENT AND RESEARCH: Calverton, NY</td>
<td>Addiction Psychiatrist, Full-Time and Part-Time</td>
</tr>
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</table>

Qualified candidates should forward their CV to Alice Perkins at OPR@Northwell.edu
INGREZZA® (valbenazine) capsules

Brief Summary: for full Prescribing Information and Patient Information, refer to package insert.

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

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

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

QT Prolongation
INGREZZA® may prolong the QT interval, although the degree of QT prolongation is not clinically significant at concentrations expected with recommended dosing. In patients taking a strong CYP3A4 or CYP2D6 inhibitor, or who are CYP2D6 poor metabolizers, INGREZZA® concentrations may be higher and QT prolongation clinically significant. For patients who are CYP2D6 poor metabolizers or taking a strong CYP2D6 inhibitor, dose reduction may be necessary. For patients taking a strong CYP3A4 inhibitor, reduce the dose of INGREZZA® to 40 mg once daily. INGREZZA® should be avoided in patients with congenital long QT syndrome or with arrhythmias associated with a prolonged QT interval. For patients at increased risk of a prolonged QT interval, assess the QT interval before increasing the dosage.

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

ADVERSE REACTIONS
The following adverse reactions are discussed in more detail in other sections of the labeling:
- Hypersensitivity
- Somnolence
- QT Prolongation
- Parkinsonism

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

Variable and Fixed Dose Placebo-Controlled Trial Experience
The safety of INGREZZA® was evaluated in 3 placebo-controlled studies, each 6 weeks in duration (fixed dose, dose escalation, dose reduction), including 645 patients. Patients were 26 to 84 years of age with moderate to severe tardive dyskinesia and had concurrent diagnoses of mood disorder (27%) or schizophrenia/ schizoaffective disorder (72%). The mean age was 56 years. Patients were 57% Caucasian, 39% African-American, and 4% other. With respect to ethnicity, 29% were Hispanic or Latin. All subjects continued previous stable regimens of antipsychotics. 85% and 27% of subjects, respectively, were taking atypical and typical antipsychotic medications at study entry.

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

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

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

<table>
<thead>
<tr>
<th>Adverse Reaction1</th>
<th>INGREZZA® (n=262) (%)</th>
<th>Placebo (n=183) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence (somnolence, fatigue, sedation)</td>
<td>10.9%</td>
<td>4.2%</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Akathisia (restlessness)</td>
<td>5.4%</td>
<td>4.9%</td>
</tr>
<tr>
<td>Balance disorders (fall, gait disturbance, dizziness, balance disorder)</td>
<td>4.1%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Headache</td>
<td>3.4%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Ataxia (ataxia, restlessness)</td>
<td>2.7%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>2.6%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Nausea</td>
<td>2.3%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Musculoskeletal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2.3%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

1 Within each adverse reaction category, the observed adverse reactions are listed in order of decreasing frequency.

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

- Endocrine Disorders: Blood glucose increased
- General Disorders: weight increased
- Infectious Disorders: respiratory infections
- Neuropsychiatric Disorders: dysphoria, dizziness, extrapyramidal symptoms (non-akathisia)
- Psychiatric Disorders: anxiety, insomnia

During controlled trials, there was a dose-related increase in prolactin. Additionally, there was a dose-related increase in alkaline phosphatase and bilirubin, suggesting a potential risk for cholestatic.

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

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

Skin and Subcutaneous Tissue Disorders: rash

DRUG INTERACTIONS
Drugs Having Clinically Important Interactions with INGREZZA®

Table 2: Clinically Significant Drug Interactions with INGREZZA®

<table>
<thead>
<tr>
<th>Monamine Oxidase Inhibitors (MAOIs)</th>
<th>Clinical Implication</th>
<th>Prevention or Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concomitant use of INGREZZA® with MAOIs may increase the concentration of monamine neurotransmitters in synapses, potentially leading to increased risk of adverse reactions such as serotonin syndrome, or attenuated treatment effect of INGREZZA®.</td>
<td>Avoid concomitant use of INGREZZA® with MAOIs.</td>
<td>Examples: tricyclic antidepressants, selegiline</td>
</tr>
</tbody>
</table>

Strong CYP3A4 Inhibitors

<table>
<thead>
<tr>
<th>Clinical Implication</th>
<th>Prevention or Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concomitant use of INGREZZA® with strong CYP3A4 inhibitors increased the exposure (Cmax and AUC) to valbenazine and its active metabolite compared with the use of INGREZZA® alone. Increased exposure of valbenazine and its active metabolite may increase the risk of exposure-related adverse reactions.</td>
<td>Reduce INGREZZA® dose when INGREZZA® is coadministered with a strong CYP3A4 inhibitor.</td>
</tr>
</tbody>
</table>

Strong CYP2D6 Inhibitors

<table>
<thead>
<tr>
<th>Clinical Implication</th>
<th>Prevention or Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concomitant use of INGREZZA® with strong CYP2D6 inhibitors increased the exposure (Cmax and AUC) to valbenazine's active metabolite compared to the use of INGREZZA® alone. Increased exposure of active metabolite may increase the risk of exposure-related adverse reactions.</td>
<td>Reduce INGREZZA® dose when INGREZZA® is coadministered with a strong CYP2D6 inhibitor.</td>
</tr>
</tbody>
</table>

Strong CYP3A4 Inducers

<table>
<thead>
<tr>
<th>Clinical Implication</th>
<th>Prevention or Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concomitant use of INGREZZA® with a strong CYP3A4 inducer decreased the exposure (Cmax and AUC) of valbenazine and its active metabolite compared to the use of INGREZZA® alone. Reduced exposure of valbenazine and its active metabolite may reduce efficacy.</td>
<td>Concomitant use of strong CYP3A4 inducers with INGREZZA® is not recommended.</td>
</tr>
</tbody>
</table>

Digoxin

<table>
<thead>
<tr>
<th>Clinical Implication</th>
<th>Prevention or Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concomitant use of INGREZZA® with digoxin increased digoxin levels because of inhibition of intestinal P-glycoprotein (P-gp).</td>
<td>Digoxin concentrations should be monitored when coadministering INGREZZA® with digoxin. Increased digoxin exposure may increase the risk of exposure-related adverse reactions. Dosage adjustment of digoxin may be necessary.</td>
</tr>
</tbody>
</table>

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

OVERDOSAGE

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

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

For further information on INGREZZA®, call 844-647-3992.
†Post hoc analysis included patients who had a baseline and a Week 6 AIMS total score Reduction in uncontrolled movements as assessed by greater than or equal to one point decrease in AIMS total score Compared to once daily regimens, timing adherence is 2% lower for two week periods of once daily regimens according to a meta-analysis of five one study in patients with chronic conditions is the simple choice to support the patient adherence

**THE SIMPLE CHOICE**

Once-daily INGREZZA is the simple choice to support patient adherence

**SYMPTOM REDUCTION**

INGREZZA 80 mg reduced uncontrolled movements in 7 of 10 patients at 6 weeks (post hoc analysis)**

**SAVINGS & SUPPORT**

$10 or less out-of-pocket is what most patients pay for INGREZZA

**WARNINGs & PRECAUTIONS (continued)**

**Parkinsonism**

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

**ADVERSE REACTIONS**

The most common adverse reaction (≥5% and twice the rate of placebo) is somnolence. Other adverse reactions (≥2% and >Placebo) include: anticholinergic effects, balance disorders/falls, headache, akathisia, vomiting, nausea, and arthralgia. You are encouraged to report negative side effects of prescription drugs to the FDA. Visit MedWatch at www.fda.gov/medwatch or call 1-800-FDA-1088.

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

**REFERENCES:**


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