L-Methylfolate: Augmenting Agent May Contribute to Agitation and Mania

Sara Robinson, MSN, RN, PMHNP-BC and John J. Miller, MD

L-methylfolate is commonly presented as a safe augmenting agent to patients with antidepressant non-response in unipolar depression with virtually no side effects. Although this is likely to be true most of the time, as with any treatment, there are risks that can be significant albeit rare. Currently, there is a paucity of published literature of double-blind placebo-controlled randomized clinical trials of the efficacy and tolerability of L-methylfolate in both unipolar and bipolar depression. This article discusses the rationale and history of L-methylfolate use in such patients, and then shares three cases that collectively suggest L-methylfolate may contribute to agitation and mania.

L-methylfolate
In humans, folate (ie, Vitamin B9) is one of 13 essential vitamins. Low serum folate and low red blood cell (RBC) folate levels are independent...
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FROM THE CHAIRMAN

We’ve Come a Long Way... Or Have We?

You know the old saying, “The more things change, the more they remain the same.” In many ways we have made great strides, and our lives are most likely easier and better than the lives of our grandparents and previous generations. But, it seems like we are still fighting the same battles.

Take, for instance, COVID-19. We have seen frightening epidemics in the past 100 years—HIV, Ebola, smallpox, Spanish flu, etc. Outbreaks are not uncommon, yet we continue to struggle with appropriate reactions to new threats. It does not take long for fear, panic, and distrust to settle in or for bad information to spread. That is why Psychiatris Times invited Dr. Nidal Moukaddam and Asim Shah to shed some light on this new virus, the pandemic, and its potential impact. Our goal is to arm you with the information you need to better educate and help your patients.

Are we faring better in the field of addiction medicine? In our Psychiatry 20/20 series, Dr. Thomas Kosten looks back at society’s approaches to addiction and comes away with mixed results. Thankfully, the US government is no longer interested in arresting and jailing psychiatrists and other addiction specialists while these clinicians help opioid-dependent patients. And, the pharmacological options to address addiction are also greatly improved. Yet, Dr. Kosten is quick to point out that we are still battling an opioid epidemic, and only time will tell if we have learned the lessons of the past.

Fortunately, there are some areas where there has been progress.

To address medication adherence, for instance, we now have psychotropic medications with improved adverse effect and efficacy profiles as well as new delivery methods. Along those lines, this month’s continuing medical education article discusses the pros and cons of long-acting injectable antipsychotics in helping to not only improve adherence but also outcomes.

So, while we may continue with similar struggles, it seems like we are taking steps in the right direction. And, cover-to-cover, Psychiatric Times will continue to provide you with timely clinical information and discussions so you, too, can make and see progress!
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**From the Editor**

Reframing Our Relationship With Pharma

John J. Miller, MD | Editor in Chief

Imagine if you or a loved one was diagnosed with cancer, and your oncologist had not learned about any new medications related to the treatment of this cancer for the past 5 years? What if your family member with a stable psychotic disorder developed severe tardive dyskinesia and, as a result, would not leave their group home due to the embarrassment caused by these involuntary movements—and their prescribing clinician had no knowledge of the two drugs that were FDA approved in 2017 to treat this movement disorder?

I love psychiatry, I love biochemistry, and I love learning. These passions collide in the arena of new drug development, which continues to deliver novel drug mechanisms of action throughout the field of medicine. In 1986, as I began my internship at the Medical Center Hospital of Vermont, with the gift of an outstandingpsychopharmacology mentor, John Ives, MD, I was able to confidently learn to prescribe all the psychiatric medications in our armamentarium at that time. To be fair, the list was rather short: monoamine oxidase inhibitors, tricyclic antidepressants, benzodiazepines, antihistamines, anticholinergics, antipsychotics, lithium, carbamazepine, valproate, and a few others.

During my internship year, I was taught the pharmacology and FDA-approved indications for two new psychiatric drugs: bupropion (which was approved on December 30, 1985 for the treatment of major depression) and buspirone (which was approved for the treatment of generalized anxiety disorder in 1986). These drugs had novel mechanisms of action and immediately were added to the hospital’s pharmacy formulary for the treatment of inpatients.

In my years of adult psychiatry residency at the Department of Psychiatry at the University of MA Medical Center in Worcester, two additional medications were FDA approved that revolutionized treatment options for many of our patients: fluoxetine and clozapine. A game changer for our patients with schizophrenia, clozapine was FDA approved in 1989 for refractory schizophrenia. Clozapine served as a paradigm shifter, and it remains the most effective treatment for refractory schizophrenia. Additionally, it prompted prompter-directed research on novel agents that would modulate serotonin along with dopamine receptors for the treatment of psychosis and mania. Within months of its FDA approval, under the guidance of my psychopharmacology supervisor, I cross titrated a patient with refractory paranoid schizophrenia from high dose perphenazine to clozapine. Meanwhile, my very first educational seminar on how to dose clozapine, and the important risks/benefits/side effects that I needed to understand before prescribing this novel drug, was presented by the pharmaceutical representative from Sandoz, who also provided me with a host of peer-reviewed, published clinical trials and information on clozapine.

**The Value of Keeping Up to Date**

In 1995, while an assistant professor...
of psychiatry at the University of Massachusetts Medical Center, I was invited to join the speakers’ bureau for a pharmaceutical company. During the subsequent 25 years, I have proudly maintained ongoing consultation collaborations with pharmaceutical companies that are focused on developing new medications with novel mechanisms of action as well as medications with improved efficacy and tolerability as compared to similar medications currently available. Once FDA approved, I continue to enjoy educating psychiatric colleagues on information important to any prescriber of a new medication: pharmacokinetics, pharmacodynamics, clinical trial results, approved indications, risks, benefits, and side effects.

Although there are many critics of physicians who collaborate with the pharmaceutical industry, I judge myself based on the feedback from the clinicians to whom I present this information. Of course, I always disclose any potential conflicts of interest when presenting a lecture or authoring a publication, which is essential.

During my tenure as a psychiatrist, I have been impressed and invigorated by the dedicated research and development in the pharmaceutical industry as well as their commitment to further understanding disease states and identifying novel medications that serve to decrease symptoms and improve the quality of life of our patients. A great example was the simultaneous FDA approval of two novel medications in 2017 for the treatment of tardive dyskinesia, a movement disorder caused by chronic exposure in a part of the brain to dopamine-2 receptor blocking agents (including all of the antipsychotics). Although tardive dyskinesia was identified in the late 1950s, and for many of our patients causes significant functional impairment, we had no treatment for it until these two medications were approved. Outside of psychiatry, the specialties of neurology, oncology, hematology, immunology, endocrinology, gastroenterology, and others have had spectacular breakthroughs in novel treatments that literally have been life-saving.

A firewall withholding new information

As clinicians with the opportunity to prescribe life-altering medications for our patients, I believe it is important to understand our biases, both positive and negative, toward Pharma. One benefit from lecturing around the country is the opportunity to meet and speak with psychiatrists, nurse practitioners, and psychiatric providers of all types, and to hear their experiences and challenges in various treatment settings. As a believer in immediate access to all new information that may improve the quality of patient care, it has been disheartening to see the pharmaceutical industry’s reluctance to share even basic data on new and expanding treatments specific to our specialty. Any new treatment is initially vetted by the FDA or other regulatory agencies. Once a novel treatment is available to us frontline clinicians, our due diligence should include an objective appraisal of this new treatment, being mindful of positive as well as negative biases that may influence our assessment, so we may determine when and how the new treatment may fit into our constantly evolving armamentarium.

As one would expect, initially the pendulum swung too far in the direction away from collaboration. In my opinion, the tragedy is that it has continued to swing away from ethical and appropriate collaboration to the current culture where the pharmaceutical industry is often demonized and ostracized.

Some generalized recurrent themes include:

- Psychiatric residents who sneak out to a lecture on a new drug express frustration that the attending/ supervising psychiatrists with whom they work have no knowledge of new medications that have been FDA approved over the past 5 to 10 years.
- A psychiatrist at a major medical center/teaching hospital who was fearful to attend a lecture program about a new medication because they were told that they would be fired if they attended any pharmaceutical industry-sponsored educational program—even though it was after hours and on their own time.
- Major medical centers/health care systems banning pharmaceutical company representatives, including highly trained medical science liaisons (usually medical doctors or doctorate level pharmacists who receive no remuneration for any resulting business, rather acting purely as a scientific resource) from even entering their buildings.
- A student with only two months remaining before completing her psychiatric nurse practitioner program at a New England teaching hospital attended a pharmaceutical company-sponsored program where she first learned about a medication that has demonstrated some unique properties helpful for a subpopulation of patients and that was FDA approved more than four years ago.
- Psychiatrists at a busy community mental health center express frustration that when their patients were admitted to several different inpatient psychiatry units, the “newer” medications were stopped, and their patients were discharged on an array of side effect-ridden older medications because they were the only options available on the hospital’s pharmacy formulary.
- Frontline prescribers are not allowed to accept medication samples from pharmaceutical companies at risk of job termination. This is unfortunate for many reasons; in my view, the biggest reason being a lost opportunity to have a month trial, at no cost, on a medication to see if it is effective before providing a prescription that will likely require an accompanying nightmare prior authorization form.

Time to move forward

When I reflect on the rich learning opportunities and experiences I have had in my role as a consultant and lecturer for various pharmaceutical companies over the past 25 years, I remain befuddled as to why many of our major medical centers/residency training programs/health care systems continue to ban the pharmaceutical industry from having any communication with their treatment providers. The majority of physicians and pharmaceutical companies, myself included, agree that during the 1990s the relationship between the pharmaceutical industry and prescribers was out of control. Too much money was being thrown around with no clear guidelines and embarrassing conflicts of interest. Appropriately, in the early 2000s, there was a major restructuring of how prescribers and the pharmaceutical industry interacted.

As clinicians with the opportunity to prescribe life-altering medications for our patients, I believe it is important to understand our biases, both positive and negative, toward Pharma. One benefit from lecturing around the country is the opportunity to meet and speak with psychiatrists, nurse practitioners, and psychiatric providers of all types, and to hear their experiences and challenges in various treatment settings. As a believer in immediate access to all new information that may improve the quality of patient care, it has been disheartening to see the pharmaceutical industry’s reluctance to share even basic data on new and expanding treatments specific to our specialty. Any new treatment is initially vetted by the FDA or other regulatory agencies. Once a novel treatment is available to us frontline clinicians, our due diligence should include an objective appraisal of this new treatment, being mindful of positive as well as negative biases that may influence our assessment, so we may determine when and how the new treatment may fit into our constantly evolving armamentarium.

In an ideal world, clinicians would be provided sufficient and mandatory time each week to research and learn about newly available treatments. My observation is that, despite good intentions, the stresses of a busy schedule, onerous documentation, returning phone calls, reviewing lab work, and conducting other patient-related correspondence ultimately collude to exhaust us by the end of the day. In this current climate, spending time with a pharmaceutical representative or attending a lecture program by a physician consultant may provide an efficient vehicle to learn the basic data and FDA-approved facts that we can then ponder, discuss with colleagues, and ultimately make our own informed decision about the potential role of new treatments in our clinical practice.

The current political climate in the United States is teaching us about the dark side of extreme partisanship—such partisanship should not exist in our honorable profession of medicine. I would suggest that it is time to reassess the black and white polarization that many academic and medical systems have erected against the pharmaceutical industry and that we resume collaboration in a manner that provides our patients with the best possible treatments.

I wonder how many years would have passed before I prescribed clozapine if I never attended that in-service by the clozapine sales representative during my residency? Yes.
As psychiatrists we must remember that comorbidities is often the rule, not the exception. This is especially true for obsessive and compulsive disorder (OCD). Not only is this important from a diagnostic point of view, but treatment may need to be pharmacologically as well as behaviorally diverse to treat all the co-existing conditions.

The articles in this Special Report address some of the more common comorbidities: bipolar disorder; Tourette syndrome; and anxiety disorders, such as panic disorder, generalized anxiety disorder, simple phobia, and specific phobia, especially in an adolescent population. In discussing bipolar disorder, the point is made that treating the mania may be enough and that adding a serotonin reuptake inhibitor could worsen mood symptoms, particularly mania. In treating Tourette syndrome, special attention should be given to Comprehensive Behavioral Intervention for tics before considering the addition of neuroleptics or the newer alpha-2 adrenergic agonist in the separate treatment of the tics in addition to the OCD.

With the article by Andrea Aguglia, MD, PhD, and colleagues, we are reminded that the brain is connected to the rest of the body. Comorbid general medical problems such as diabetes, hypertension, and obesity may be related to OCD treatment or precipitated by environmental stressors as a result of living with the disorder. Some of these environmental stressors include living lonely isolated lives and engaging in unhealthy behaviors, such as alcohol use and smoking, to deal with the anxiety related to OCD symptoms.

Pregnancy is another type of stress that cannot be overlooked as a cause or exacerbation of OCD. Erika L. Nurmi, MD, PhD, and Carol A Mathews, MD, address postpartum OCD and make some specific recommendations for treatment during and after pregnancy. In particular, they note physiological and psychodynamic issues around breastfeeding. For example, new mothers may obsess about harming the newborn from exposure in utero or in breast milk because of the OCD medications they are taking.

Meanwhile, Jon E. Grant, MD, and Samuel R. Chamberlain, MD, provide hope in what we have learned most recently about the neurobiology of OCD but also challenges for us to fill in the blanks about what we still do not know. They make note of newer regions outside of the orbitofrontal loop that might be part of the neurophysiology of OCD.

Although there is still more to say and learn, together these articles provide up-to-date information that clinicians can turn to when making treatment decisions for OCD, its comorbidities and related disorders.

Dr. Pato is Co-Director, Institute for Genomic Health (IGH) and Professor and Vice Chair for Research, Department of Psychiatry, SUNY Downstate, Brooklyn, NY. She reports no conflicts of interest concerning the subject matter of this Special Report.
Update on Tourette Syndrome

Erika L. Numri, MD, PhD, and Carol A. Mathews, MD

CASE VIGNETTE

“Johan,” 16 years old, has had chronic eye tics since he was 6. Over the years, he has manifested multiple tics, including grunting, facial movements, and arm and leg movements. In early adolescence, he developed a complex and ritualized sequence of tics that involved touching other people, shrieking, posturing, and hand and leg movements. The tics were often triggered by unwanted intrusive thoughts or obsessions related to impending harm to himself or others.

Behavioral therapy was not of benefit, and several medication trials were attempted. He had a partial response to a combination of a selective serotonin reuptake inhibitor and a typical neuroleptic. The tics subsided greatly after age 15, although he continues to have mild tics occasionally. Depression that developed at age 16 was successfully treated with a modification of the SSR1 dose.

Tourette syndrome (TS) and other tic disorders are neurodevelopmental disorders that begin in early childhood and are defined by the ongoing presence of tics (ie, sudden repetitive movements or vocalizations). Tics may occur in any muscle group, but typically begin with the eyes. Over time, tics become more complex, often include vocal tics, and affect other muscle groups, usually in a rostral to caudal progression.

Simple tics include movements such as eye blinking or rolling, gazing, grimacing and jerking, and vocalizations such as grunting, coughing, clicking, and throat clearing. Complex tics include touching, hitting, jumping, simulating an action, and speaking words and phrases. Echophenomena, the mimicking of words (echolalia) and gestures (echopraxia); paliphenomena, the repeating of words (palilalia) and gestures (palipraxia); and coprophenomena, the mimicking of words (coprolalia) or gestures (copropraxia) can also occur. These are often associated with comorbid OCD. While coprophenomena are pathognomonic for TS, their frequency is exaggerated by the media; in reality, only 10% of patients with tic disorders display these symptoms.

Tics are preceded by premonitory urges, which are uncomfortable sensations that are relieved by the execution of the tic. Adults may describe tics as a volitional response to an irresistible impulse, rather than an involuntary movement. Although tics predominantly occur during wake time, they can also occur during sleep, highlighting the lack of volition.

Diagnosis and differential diagnosis

DSM-5 criteria for TS require childhood onset of two or more motor tics that occur frequently throughout the day nearly every day for longer than one year and at least one vocal tic at any point. Pure motor or phonic tics are diagnosed as persistent motor or vocal tic disorder. When tics occur for a shorter duration than one year, a provisional tic disorder diagnosis is given. Mild tics that spontaneously resolve without impairment are common (25%) in childhood and do not necessarily indicate an increased risk of future psychopathology.

Tic disorders have unique characteristics that differentiate them from other neurologic and psychiatric disorders. Tics are repetitive and predictable but non-rhythmic movements, usually asymmetrical. They are multifocal, rapid and preceded by an urge or other sensation. With effort, they are suppressible. Tic persistence and severity fluctuates and can be worsened by stress, boredom, and fatigue; tics can subside when the individual is absorbed in an enjoyable or demanding activity. Stereotypies, common in autism spectrum disorder, can mimic tics, but typically occur at a younger age, are soothing rather than uncomfortable, and are ego-syntonic. Compulsions, which are also complex repetitive behaviors, are voluntary and marked by the presence of distressing or anxious thoughts (eg, obsessions) preceding the behavior, rather than a physical sensation.

Comorbidity and associated symptoms

In TS, comorbidity is the rule rather than the exception. The majority of patients have at least one comorbidity and more than half have 2 or more psychiatric comorbidities. These comorbidities are often more impairing than the tics.

ADHD is the most common comorbidity, closely followed by OCD; anxiety and depression are also frequent (Table 1). Social deficits, learning disorders, sleep problems, and rage episodes contribute to academic difficulties. Tics decrease in severity during the transition to adulthood, often dramatically, but comorbid attentional, mood, anxiety, and rage episodes contribute to academic difficulties. Tics decrease in severity during the transition to adulthood, often dramatically, but comorbid attentional, mood, anxiety, and sleep symptoms often persist.

While comorbidity worsens prognosis, it does not explain all TS-associated impairment. Impaired social functioning and peer relationship problems, emotional lability, behavior problems, and lower quality of life occur in TS independent of comorbidity.

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD</td>
<td>~50%</td>
</tr>
<tr>
<td>OCD</td>
<td>30% to 40%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>15% to 20%</td>
</tr>
<tr>
<td>Depression</td>
<td>5% to 20%</td>
</tr>
<tr>
<td>Rage</td>
<td>20% to 60%</td>
</tr>
</tbody>
</table>

Epidemiology and natural course

The prevalence of chronic tic disorders is between 1% and 3%, and the prevalence of TS is approximately 0.8%.1 TS affects more males than females (4 to 1), but it is undiagnosed in about half of all children who have it.2 The average age of onset is 5 to 6 years, and 96% of patients experience onset by age 11.3 TS is usually diagnosed 2 to 3 years after onset, and peak severity occurs around puberty.

Typically, tics diminish during adolescence or early adulthood, although a small minority of patients have an intensifying course without improvement. Even with minimal tics and comorbidities entering adulthood, some patients continue to have difficulties with executive functions in daily life, including planning, education, and relating to their peers and, thus, require continued support.

Etiology: genetic and environmental influences

Tic disorders are strongly genetic with heritability estimates between 70% and 80%.4 However, environmental factors clearly also play a role in their development and expression. Tic disorders are polygenic; in most patients, hundreds of genes or alleles of small effect act in aggregate to cause increased susceptibility to tic development.

Approximately 58% of the risk for TS is conferred by common variants distributed across the entire genome, while 20% is explained by rare var-
Multiple risk genes for TS include those involved in cell adhesion and synapse formation, intracellular signaling, chromatin regulation, and histamine signaling (Table 2). Rare damaging variants in about 400 genes contribute risk in 12% of people with TS and copy number variants that are also seen in other neurodevelopmental disorders account for a small percentage of TS but confer substantially increased risk when present.

TS can fundamentally be conceptualized as a disorder of “problematic brakes in the brain;” dysfunction within the motor and limbic components of the cortico-striatal-thalamic-cortical loop is hypothesized to underlie an inability to suppress unwanted movements, and impulses. Cortical thinning in sensorimotor areas may also play a role in TS development. Tic disorders are associated with neurocognitive dysfunction, specifically deficits in response inhibition and attentional processing.

Despite strong genetic underpinnings, it is important to note that tics are significantly influenced by the environment. Tic symptom severity is associated with paternal age, maternal prenatal smoking, low birth weight, and obstetrical complications as well as stress such as tests at school, peer and family conflict, excitement (eg, engaging in an exciting activity), and physical illness or fatigue.

**Treatment options and strategies**

Recent practice parameters were published by the American Academy of Neurology with the goal of advising clinicians when and how to treat tic disorders; the treatment recommendations in this review are in line with these guidelines. Treatment plans should be individualized and developed collaboratively with the patient and family. Screening for comorbidities is essential, including screening for suicidal ideation, which occurs at an elevated rate in TS. Despite many treatment options, families should understand that treatment infrequently results in complete cessation of tics. Several validated rating scales are available to measure and track tic severity and treatment response, such as the Yale Global Tic Severity Scale (YGTSS) and Parent Tic Questionnaire (PTQ).

**Psychoeducation and resources.** Although tics can be alarming to parents, most do not need treatment; psychoeducation and parent coaching is usually adequate. Although parents may be told to ignore tics when they first manifest and may be reassured that their child will grow out of it, a more complete message would be to convey the message that tics are “no big deal,” that they are not shameful, and that it is okay to discuss them. For chronic tics, education in the school with teachers and classmates can be extremely effective in improving the child’s social experience and reducing stigma. Families can be referred to the Tourette Association of America (tourette.org), which has resources and guidance on talking about tics at school.

**Behavioral treatment.** If tics produce significant impairment or distress, several treatment options are available. First-line treatment for tic disorders is comprehensive behavioral intervention for tics (CBIT) guided by a trained therapist. CBIT has two components: the functional assessment identifies and alters factors in the environment that trigger or reinforce the tics so that a tic neutral environment is created; and the habit reversal treatment (HRT) uses a competing response to train patients to tolerate their urge to break the urge cycle. HRT is as effective as medication but requires practice, so motivation, commitment, and parental involvement are key factors.

**Pharmacotherapy.** When behavioral interventions are inadequate, pharmacotherapy may be warranted. Neuroleptics are the only FDA-indicated medications for tics; those with the strongest data include aripiprazole, risperidone, ziprasidone, haloperidol, and pimozide. Neuroleptics for tics can be used at a fraction of the doses used to treat psychotic disorders, although adverse effects (eg, motor, metabolic) still make this class of medications less desirable as a first-line treatment. Despite a higher adverse effect burden, severe impairing tics warrant consideration of a neuroleptic.

Although not currently FDA-approved, the alpha-2 adrenergic agonists guanafacine and clonidine, which are used to treat attention deficit/hyperactivity disorder, are often prescribed first-line for tics, given their favorable risk-benefit ratio. As these medications are sedating, patients and parents should be warned about sleepiness during the initial adjustment period. Monitoring vital signs for hypotension and bradycardia during titration is advised. In addition to treating comorbid attentional symptoms, alpha agonists are as effective for tics as neuroleptics, particularly with comorbid ADHD.

Other medication options for moderate to severe tics include dopamine depleters (tetraabenazine, deutetramazine, valbenazine), GABA modulators (benzodiazepines, topiramate, baclofen), and dopamine agonists.

Local botulinum toxin (botox) injection can relieve painful or dystonic simple tics but is limited in scope and must be repeated quarterly. Cannabinoids like tetrahydrocannabinol (THC) and cannabidiol (CBD) are under investigation, but given risks to

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**Table 2. Risk genes for Tourette syndrome**

<table>
<thead>
<tr>
<th>Risk gene(s)</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRXN1, CNTN6, SLITRK1, CELSR3, FEN</td>
<td>Cell adhesion and synapse formation</td>
</tr>
<tr>
<td>WW1C</td>
<td>Intracellular signaling</td>
</tr>
<tr>
<td>NIPBL</td>
<td>Chromatic regulation</td>
</tr>
<tr>
<td>HDC</td>
<td>Histamine signaling</td>
</tr>
</tbody>
</table>

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**Fast Facts on Tourette Syndrome**

**Phenomenology**

- Tic disorders are neurodevelopmental disorders characterized by involuntary movements and vocalizations, as well as frequent psychiatric comorbidity.
- Screening for common comorbidities, such as ADHD, OCD, anxiety, and depression in patients with tics is essential.
- In addition to tics and psychiatric comorbidities, learning, behavioral, social and sleep problems can interfere with academic functioning.

**Epidemiology**

- Chronic tic disorders affect up to 3% of the worldwide population, males more than females.

**Prognosis**

- Tics have a prepubertal onset (mean age 6 years), a waxing and waning course, peak symptoms at puberty and decline over adolescence.

**Differential diagnosis**

- Tic disorders are differentiated from other disorders by movement character and pattern, premonitory urge, voluntary suppression, suggestibility, comorbidity, and exacerbating factors.

**Etiology**

- TS is a strongly genetic multifactorial disorder that is sensitive to environmental influences.
- TS is thought to arise from disinhibition in cortico-striatal-thalamic-cortical brain circuits.
MARCH 2020

Common case scenarios and recommended strategies

5-year-old boy referred with eye blink, sniffing, and throat clearing tics after his parents brought him for medical evaluation for allergies

Recommended initial approach

- Provide psychoeducation, resources, and reassurance for parents
- Teach function-based assessment and tic neutral environment
- Monitor over time

16-year-old girl with mild motor tics and prominent, impairing OCD, doing poorly in school

Recommended initial approach

- Provide psychoeducation and resources for patient and parents
- OCD: refer for exposure-response prevention (ERP) therapy, consider SSRI (assess level of distress and impairment)
- Tics: teach function-based assessment and tic neutral environment, consider CBIT if tics become impairing or distressing
- Assess/screen for common comorbidities (especially ADHD and learning disabilities)

12-year-old boy with moderate TS, ADHD, and anxiety, bullied at school and struggling academically

Recommended initial approach

- Provide psychoeducation, resources, and psychosocial support for patient and parents (teach about speaking to the school/classroom about TS)
- Tics: refer for CBT, consider alpha agonist
- ADHD: rating scales/assessment, teach behavioral strategies, consider alpha agonist versus stimulant
- Anxiety: consider referral for CBT, consider SSRI
- Screen for common comorbidities (especially depression)

10-year-old boy with severe Tourette with coprolalia, high-functioning autism spectrum disorder, moderate OCD, and behavioral problems (including rage episodes) with frequent tantrums at home and regularly sent home from school for aggression

Recommended initial approach

- Provide psychoeducation, resources, and psychosocial support for patient and parents as well as parent training and social skills resources
- Tics: consider CBIT if child motivated and able to engage, consider alpha agonist versus antipsychotic
- OCD: consider exposure-response prevention if child motivated and able to engage, consider SSRI after tics addressed
- Screen for common comorbidities (especially ADHD and depression)

The natural course of TS is such that symptoms frequently improve or worsen over time, even when untreated. Therefore, careful assessment over sufficient intervals without acute environmental triggers may be required to judge whether further medication optimization is indicated. As the patient matures, it is also important to evaluate whether medication is still necessary. After a period of sustained stability, gradual taper with close observation is advisable.

Neuromodulation. Patients with debilitating refractory tics may be candidates for experimental surgical treatments such as deep brain stimulation. Given the remitting course of TS in adolescence and the high rate of adverse events, it is generally not an appropriate intervention for youth. Trials exploring transcranial magnetic stimulation (TMS) in TS are under way and could represent a less invasive option.

Conclusion

Tic disorders are common neurodevelopmental disorders that have a waxing and waning course, which generally improve in adulthood. Although tics can be debilitating in a minority of patients, the psychiatric comorbidities that are seen in the majority of patients contribute to most of the functional impairment. Thus, frequent screening for and treatment of psychiatric comorbidities is critical to improving quality of life for individuals with TS and other chronic tic disorders. Participation in activities to promote acceptance, social support, self-efficacy, resilience and life satisfaction can be some of the most important interventions in managing TS.

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“Frequent screening for and treatment of psychiatric comorbidities is critical to improving quality of life for individuals with TS and other chronic tic disorders.”
When Baby and OCD Are on Board: Assessment and Treatment Issues

Shelly Kucherer, MD,
and Nancy Byatt, DO, MBA

CASE VIGNETTE

“Andrea,” a 28 year old is 6 months postpartum. She presents to the psychiatric department (ED) seeking help for anxiety. She notes that she was reluctant to come to the ED because of fear of being judged. Yet ultimately came because her husband has noticed that she is spending less and less time with the baby and he is becoming increasingly worried about her.

Andrea reports that she has been having thoughts of drowning her child since she was 1 month postpartum. She has been avoiding washing dishes for fear that she will spray the water on her baby and cause her harm. She does not want to harm her child, and reports these thoughts are scary and distressing, but she cannot get the drowning images out of her head. The thoughts are frequent and can persist for up to 4-5 hours every day. She is so worried that she will act on these thoughts that she has been asking her mother or her partner to bathe her daughter, and she is relieved not to have to do it herself. Aside from adapting to life with a newborn, she reports no other major current stressors and appreciates the support from her husband and her parents.

On psychiatric review of symptoms, she does not endorse current mood symptoms. She has a history of depression; in her first year of college she was treated with fluoxetine and cognitive behavioral therapy, after which the symptoms resolved. She stopped fluoxetine 6 months later and has felt well since then.

She has no history of harming herself or others and no other psychiatric history, including no history of obsessive compulsive disorder. She reports significant anxiety and feeling on edge because of the thoughts of drowning her baby. Aside from recent non-complicated vaginal delivery, her medical history is also significant for hypothyroidism, for which she continues to take levothyroxine.

SIGNIFICANCE FOR PRACTICING PSYCHIATRISTS

Perinatal obsessive-compulsive disorder is common; women often find it challenging to discuss their OCD symptoms with clinicians. Stress and anxiety in pregnancy can lead to distress for the mother and changes in fetal and infant development. Perinatal OCD is associated with negative consequences on social support, infant development, and mothering.

OCD in the general population often differs from OCD in the perinatal period.

Diagnosis and comorbidity

Women with postpartum OCD often have obsessional thoughts about harming their child, which can be scary for both the patient and their health care provider(s). As previously noted, patients with OCD do not typically act on their intrusive thoughts. It is important to differentiate intrusive thoughts of harming the infant that are part of OCD or depression versus thoughts of harm secondary to postpartum psychosis.

Risk factors

Risk factors for perinatal OCD include personal history of depression, primiparity, obsessive-compulsive personality disorder, avoidant personality disorder, obstetric complications during pregnancy or delivery, and somatic illness. Family history of mood and substance use disorders are more common than family history of obsessive-compulsive disorder in women with perinatal OCD.

Prevalence and epidemiology

Perinatal (ie, pregnancy or in the year after birth) obsessive-compulsive disorder (OCD) is common, with a prevalence of 2% during pregnancy and 2.5% in the postpartum period.1 In perinatal OCD, the onset of OCD symptoms is during pregnancy or the postpartum period. Subthreshold OCD symptoms that can involve intrusive thoughts about harming the newborn or fetus also are prevalent, and prior research reports that 49% to 69% of women have such thoughts during the perinatal period.2

OCD in the general population often differs from OCD that presents in the perinatal period. In perinatal OCD, most obsessions involve the fetus or newborn, and the obsessions are often accompanied by intrusive thoughts and fears of harming the newborn. Compulsions often manifest as avoidance of the newborn or things related to their obsessions (eg, water, in the Andrea’s case).3 Similarly, women who develop OCD during pregnancy tend to have contamination obsessions and rituals such as washing and cleaning. To meet the diagnostic criteria for OCD, the symptoms need to be severe enough to cause impairment.

When the onset of OCD symptoms occurs postpartum, it tends to occur rapidly, usually beginning within 4 weeks postpartum. Symptoms can also start during pregnancy, although usually the onset is more gradual if occurring during the prenatal period as compared to during the postpartum period.4

Detection and assessment

Many women with perinatal OCD are hesitant to disclose symptoms to medical providers due to stigma and concerns about child protective services. It is important to approach women using an empathic strength-based approach and to ask specifically about intrusive thoughts. Women may prefer to discuss intrusive thoughts in general without revealing specific details. Asking how they are managing the thoughts can help facilitate the assessment, because women may be more comfortable discussing it when approached in this manner. For example, stating “This sounds so stressful and scary, how are you managing to spend time with your baby with all this happening?” instead of “Why have you not been spending time with your baby?”

Women with OCD are at low risk of acting on intrusive thoughts because, as in Andrea’s case, the thoughts of harming their newborns are ego dystonic and scare women, thus they have no intention of harming their newborn. Given this, referral to child protective services or referral the psychiatric emergency room is not usually necessary. If done inappropriately, such referrals can be perceived as punitive by women and their families, exacerbating OCD symptoms and creating barriers for participating in outpatient mental health treatment.5

Diagnosis and comorbidity

Women with postpartum OCD often have obsessional thoughts about harming their child, which can be scary for both the patient and their health care provider(s). As previously noted, patients with OCD do not typically act on their intrusive thoughts. It is important to differentiate intrusive thoughts of harming the infant that are part of OCD or depression versus thoughts of harm secondary to postpartum psychosis (Table). Postpartum psychosis is ego syntonic and often is associated with hallucinations, delusions, and negative symptoms of psychosis such as disorganization and changes in mood that are not seen in OCD.1 Postpartum psychosis is rare but is considered a psychiatric emergency and occurs most frequently in women with bipolar disorder.6

Women with perinatal OCD are at higher risk of depression, especially significant when intrusive thoughts about hurting the newborn are present. Many women with perinatal OCD also develop depression, and obsessions are common within perinatal depression as well.7

CASE VIGNETTE, CONTINUED

After a full assessment, the psychiatrist in the ED diagnoses perinatal OCD. The psychiatrist provides psychoeducation and reassures Andrea that the risks of harming her baby are low and that what she is having are intrusive thoughts that are common in OCD. The psychiatrist talks to Andrea about various treatment options, including exposure response prevention therapy (a type of cognitive behavioral therapy) and medication options. Andrea is eager to start exposure response prevention therapy. Andrea, however, is much more cautious about medications, despite...
her severe symptoms, because she is currently breastfeeding. She reports she has talked to friends who were told that medications were too risky throughout the perinatal period and when breastfeeding and would like to know more about the risks and benefits of medications prior to starting one. She said that she has several friends who were told that they needed to stop their medications immediately after getting pregnant and could not start them again until after they finished breastfeeding, and she worries about the risks.

### Treatment issues

A patient-centered approach is important for the treatment of OCD, and both the provider and patient should feel comfortable with the plan. Cognitive behavioral therapy either alone or with selective serotonin reuptake inhibitor (SSRI) medications is effective and should be offered. SSRIs alone can also be effective. In cases of treatment-resistant OCD in the perinatal period, when treatment with SSRI medication or serotonin norepinephrine reuptake inhibitors (SNRIs) has not been effective, augmentation with quetiapine also has been shown to be effective.

When leveraging pharmacotherapy, it is important to discuss the risks and benefits of the medications during the perinatal period, which includes potential effects to the fetus if the woman is pregnant and effects in postpartum if the woman is breastfeeding. When discussing medications, it is also important to discuss the risks of untreated perinatal OCD, which carries risk in itself. Stress and anxiety in pregnancy can lead to distress for the mother and can lead to changes in fetal and infant development. Perinatal OCD has been associated with negative consequences on social support, infant development, and mothering.8

During pregnancy, antidepressants are evidence-based treatment option and are not considered major teratogens.9 When considering medications in the postnatal period, if a woman is breastfeeding, it is important to also discuss that breastfeeding is considered generally safe with low blood levels of SSRIs passed through the breastmilk.9 When considering a medication, it is important to consider what has and has not been helpful to the woman in the past to avoid multiple exposures and medication trials. There are many databases that can be helpful for information on medications during the perinatal period for patients and clinicians who have more questions, including databases such as MotherToBaby,10 Lactmed,11 and ReproTox.12

### Conclusion

Given its prevalence and its negative impact when left untreated, it is imperative to recognize, assess, and treat perinatal OCD using a strengths-based approach. Doing so carries the potential to improve maternal and child outcomes and have a transgenerational impact.

Dr Kucherer is Assistant Professor of Psychiatry at the University of Pittsburgh Medical Center, Western Psychiatric Hospital. Drs Byatt and Dr Kucherer have nothing to disclose regarding the subject matter of this piece. Dr Byatt has served on the Medscape Steering Committee on Clinical Advances in Postpartum Depression. She has received honoraria from Medscape and Miller Medical Communications. She has served on Advisory Boards for Sage Therapeutics, and is a Council Member of the Gerson Lehrman Group. She also has served as a consultant for Ovia Health, Sage Therapeutics or their agents, and has received speaking honoraria from Sage Therapeutics.

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The New Game of Microbiology Clue

Continued from cover

Although pharmaceutical companies and countries are looking into vaccinations and curative treatment for coronavirus infection, currently there is nothing available; thus, precautions against transmission and early supportive treatment is key. Psychi-atrists must have a basic understanding of the pathophysiology of coronavi-ruses in order to be able to accurately explain and discuss those issues with their patients, especially as mental health ramifications are expected.

Exploring the coronavirus: what is it?
Coronaviruses, belonging to the Coronaviridae family, are single-stranded positive-sense ribonucleic acid (RNA) viruses that thrive in animals, which are their natural carriers. The only coronaviruses previously known to infect humans were HCoV-229E, HCoV-OC43, HCoV-NL63, and HKU1, as well as the two infamous relatives of 2019-nCoV— the severe acute respiratory syndrome (SARS) and the Middle East respira-tory syndrome (MERS), responsible for outbreaks in 2002-2003 and 2012, respectively. Alpha-coronaviruses and betacoronaviruses infect mammals (eg, bats) whereas gammacoronavi-ruses and deltacoronaviruses are more prone to cause fish and bird infections (Table). Animal to human—zoonotic—transmission is not the norm for coronaviruses, but prior coronavirus outbreaks in animals have been economically damaging.

It is unclear why more zoonotic epidemics have been occurring of late. However, it is hypothesized that global climate factors may be related and similar to viral mutations linked to pandemic capacity (ie, genetic drifts in a wide outbreak in animals may essentially lead to better virus survival rates in humans).

In the case of COVID-19, the transmission is suspected to have occurred at the Wuhan Huanan Seafood Wholesale Market, although the exact carrier species has not been determined. From this point, the main 2019-nCoV contagion has been hu-man-to-human transmission. Symptoms have ranged from mild to severe, with most patients reporting fever, dry cough, myalgia, fatigue, and diarrhea. Gastrointestinal symptoms have been present, although less frequent than with SARS.

Variations in innate immune response
Why do some people get sicker than others? Coronaviruses have an RNA genome, similar to the influenza virus (responsible for the flu) or the respiratory syncyntial virus (RSV). The immune system recognizes the RNA as foreign and triggers the immune response responsible for fighting the virus (ie, production of interferons and pro-inflammatory cytokines), and then clearing the foreign entity out of the body. A review of the exact immune responses are beyond the scope of this manuscript. However, the reader is encouraged to remember that the immune system is highly adaptable and modifies its metabolism and existing balance to fight expected threats (for an excellent review, see Kikkert). Unfortunately, the virus exploits the host’s immune system, mimicking certain innate components to hide while replicating, which makes the immune system less able to effectively fight the invasion. Viruses may also halt cellular replication and use existing cellular resources to prioritize viral replication. The balance between immune response and viral replicative success ultimately determines disease outcome.

Certain populations are known to be vulnerable to COVID-19, such as infants, the elderly, and those with immunocompromised systems or pre-existing medical issues, who are at increased risk for severe repercussions from infections and, thus, more likely to develop sepsis and possibly death; worse outcomes could also be related to an overactive immune response. Cytokine storm, a term referring to over-production of inflammatory cytokines, was found more often in patients suffering from COVID-19 who ended up in intensive care, but causal factors are not fully understood. Thus far, there is no way to predict who will have an exaggerated immune response besides looking for the previously noted clinical, non-specific factors.

Cleaning and disinfection to prevent transmission
Concern arises about transmission between various individuals but also about persistence of the virus on inanimate surfaces, such as mailed packages or in health care settings. As such, WHO has provided a set of recommendations for disinfecting surfaces. While the persistence of 2012-nCoV is not fully understood, it has been shown that other strains of coronaviruses stay viable for up to 9 days on surfaces (unless disinfected).

Testing of the recommend WHO formulations against various viruses revealed effectiveness. Ethanol, sodium hypochlorite, and glutaraldehyde have been found most effective; a concentration of 70% ethanol is adequate for small surface disinfection. Patients inquiring about cleaning should be cautioned about using gloves with bleach (sodium hypochlorite) and other substances. Special attention should be paid to patients with cleaning compulsions, who get skin damage from excessive cleaning product exposure. (The worsening of obsessive-compulsive disorder is discussed in the accompanying article.)

The CDC recommended precautions include the use of a facemask for suspected patients/affected individuals (not for healthy individuals) and hand washing with soap and water for 20 seconds or using any sanitizers with at least 60% alcohol content. This especially should be done after using the restroom; after blowing one’s nose, coughing, sneezing; and before and after eating.

Although the coronavirus may have infected thousands of people, it is important to put its impact into perspective. For instance, according to the CDC, influenza already has affected 19 million people this year.
The presence of COVID-19 can be assessed by a newly released real time reverse transcription-polymerase chain reaction (RT-PCR) test. Of course, here in the US, clinicians are encouraged to contact and collaborate with their state or local health department for any diagnosed or suspected cases.

While there is no specific treatment for COVID-19, WHO has issued an interim guidance document, which is available online at www.who.int/. Meanwhile, there have been treatment attempts with various antivirals (e.g., remdesivir, lopinavir-ritonavir, interferon-a 2b) developed for previously known viral agents. None of these have been studied in randomized controlled trials for COVID-19 and results are not yet conclusive.

The current recommendation for patients requiring hospitalization is isolation and supportive care, including oxygen therapy and fluid management. Administration of antivirals for treatment of secondary bacterial infections and avoiding secondary end-organ damage also may be needed for some patients. Care must be taken to discourage patients from seeking untested, potentially dangerous treatments such as the counter/concoctions.

Without specific treatments, the emphasis has been on limiting new exposures, which is where infection and quarantines come into play. Currently, the incubation period is thought to be 2 to 14 days, so limiting exposure to individuals with suspected infection during that time, and within the active symptom period, is the first and most basic step in preventing further spread of the virus.

The working incubation period takes a few things into consideration. In a systematic review of nine viral agents of public health importance, Lessler and colleagues1 found most coronaviruses had a median incubation time of 3 to 4 days. Among affected individuals from China, the median incubation period has been about 5 days, with a range of 4 to 7 days and a 95% percentile of 12.5 days; thus, the typically imposed 14-day incubation period. Although some anecdotal reports suggest a longer incubation, the CDC believes data show 14 days is the top amount needed.

Psychiatric and societal implications

The coronavirus has largely dominated the news and the minds of people across the globe for the last month. In the following article, we discuss its impact on mental illnesses, stigma, and discrimination in our communities.

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Anxiety and Stress Disorders

Psychiatrists Beware!
The Impact of COVID-19 and Pandemics on Mental Health

Nidal Mukaddam, MD, PhD and Asim Shah, MD

It’s easy to blame, it’s easy to politicize, it’s harder to tackle a problem together and find solutions together. — WHO Director-General Tedros Adhanom Ghebreyesus, PhD, MSc

I nfectious pandemics and the spread of organisms across countries and continents have been facilitated by global changes in geography, climate, and an increase in travel and international exchange. COVID-19, the infection caused by the novel coronavirus detected in December 2019, is now affecting more than 27 countries, raising concerns of widespread panic and increasing anxiety in individuals subjected to the (real or perceived) threat of the virus. Importantly, these concerns arise with all infections, including the flu and other agents, and the same universal precautions are needed and indicated for safety and the prevention of further transmission. However, media coverage has highlighted COVID-19 as a unique threat, rather than one of many, which has added to panic, stress, and the potential for hysteria.

Pandemics are not just a medical phenomenon; they affect individuals and society on many levels, causing disruptions (Figure). Stigma and xenophobia are two aspects of the societal impact of pandemic infectious outbreaks. Panic and stress have also been linked to outbreaks. As concerns over the perceived threat grow, people may start to collect (and possibly hoard) masks and other medical supplies. This is often followed by anxiety-related behaviors, sleep disturbances, and overall lower perceived state of health. Individuals with mental illness may be particularly vulnerable to the effects of widespread panic and threat.

Chronic disease, including chronic infectious diseases such as tuberculosis and human immunodeficiency virus (HIV), are associated with higher levels of mental disorders as compared with the general population. Studies show depression rates usually soar after infections (e.g., herpes exposure and anthrax scares). Although the effects of the coronavirus on mental health have not been systematically studied, it is anticipated that COVID-19 will have rippling effects, especially based on current public reactions. Psychiatrists are uniquely situated to help both their patients and the greater community understand the potential impact of the virus and help families, patients, and society deal with this latest threat.

Stigma, medical mistrust, and conspiracies

Epide mics lead to stigmatization of affected individuals, authority figures, and health care professionals; sadly, this trend has been seen in multiple countries and with multiple infectious agents. With COVID-19, men and women of Asian descent, specifically Chinese, are the victims of social stigma and xenophobia, with high levels of politicization and threats online and in personal interactions. As with most stigma-laden interactions, the process unfolds because of limited information, hasty and unidimensional assessments, and a defensive formulaic response. It is imperative that all health care professionals, especially psychiatrists, act as the voice of reason and help disseminate proper, evidence-based information.

“Medical mistrust” refers to a lack of trust in medical treatment and administration. It results in a lower use of health care resources and poorer management of health conditions (coupled with potential misuse at times of crisis). Moreover, medical mistrust has been used to explain some racial and ethnic health care disparities. It has been linked to a variety of diseases.
and conditions, including cancer, autism, and HIV.

During infectious pandemics, medical mistrust has been linked to conspiracy theories. In one US study, up to half of those surveyed endorsed belief in at least one health-related conspiracy theory. At its extreme, medical mistrust can lead to movements such as anti-vaccination trends, which have been linked to measles outbreaks. Mistrust of medical organizations can reinforce stigma and perceived discrimination and result in lower adherence to health recommendations. Clinicians must maintain a scientific, fact-based, and neutral presentation of recommendations while emphasizing the importance of overall infection control practices in the wake of COVID-19.

Anxiety and obsessive-compulsive disorders

We anticipate the effects of infectious disease threats to manifest as sheer anxiety and panic: worry about getting an infection, worry about loved ones getting ill, and worry when related symptoms—even minor—are present. The absence of a definitive treatment for coronavirus easily exacerbates anxiety. In most cases, these anxiety symptoms do not reach diagnostic thresholds for a DSM-5 diagnosis; however, patients will benefit from reassurance and education.

Contamination obsessions—unwanted, intrusive thoughts that a specific contamination is present and requires immediate remediation—are present in up to 75% of patients with OCD. More intense sensory experiences (pseudo-hallucinations) have been found in up to 75% of patients with OCD. More intense sensory experiences (pseudo-hallucinations) are related to worsened control over compulsions and poorer insight. This may increase sensitivity to the plex effects of climate changes can affect patients as well as confuse even an overall healthy person. At the intersection of psychosis and obsessiveness is delusional parasitosis, also referred to as monosymptomatic hypochondriacal psychosis, Ekbom syndrome, and delusional infestation. Essentially, the patient believes that he or she is infected with an organism that evades detection and treatment, and, thus, causes continuous suffering. This syndrome was described as early as 1636 by sir Thomas Browne, who referred to it as Morgellons disease.

A concerning clinical feature of delusional infestation is its occurrence in multiple family members (eg, folie a deux). Delusional infestation development in the context of pandemics has not been studied. Conceivably, increased cases may develop as more individuals focus on far-fetched, unlikely infections because of easy access to unverified information on the internet. To address delusional parasitosis, clinicians should rule out organic causes and reassure the patient that there is no infection or infestation.

Conclusions

The current COVID-19 outbreak is spurring fear on a societal level. On an individual level, it may differentially exacerbate anxiety and psychosis-like symptoms as well as lead to non-specific mental issues (eg, mood problems, sleep issues, phobia-like behaviors, panic-like symptoms). We urge our colleagues to spread sound infection control practices and help their communities maintain civil, courteous, and rational communication. A low index of suspicion of mental distress can help in early detection and treatment and spare patients much suffering.

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risk factors for major depressive disorder (MDD); they also are associated with more severe depressive episodes and poor response to antidepressant treatment. Maternal folic acid deficiency prior to conception and throughout pregnancy has been shown to increase the risk of neural tube defects and congenital abnormalities in the developing fetus, as well as peripheral neuropathy and anemia in the mother. Ongoing studies in psychiatry and obstetrics support the use of oral dosing with the bioactive form of folate, L-methylfolate. L-methylfolate is FDA approved as a medicinal supplement for antidepressant augmentation. The use of L-methylfolate allows the clinician to bypass a critical metabolic step in folate’s transformation to L-methylfolate, specifically the reduction of methylenetetrahydrofolate to L-methylfolate by the enzyme methylenetetrahydrofolate reductase (MTHFR). MTHFR is the rate limiting step in this process, and significantly, MTHFR enzymatic activity has a wide range of function depending on its genetic polymorphisms at three nucleic acid sites, the most significant being: C677T (good activity), C677T (decreased activity), and T677T poor activity.

L-methylfolate is the only form of folate that can cross the blood-brain barrier, where it plays an essential role in the one carbon cycle metabolic pathway that is required for the production of the monoamines serotonin, dopamine, and norepinephrine.

Evidence for efficacy and tolerability

Papakostas and colleagues undertook a randomized study of L-methylfolate as adjunctive therapy in patients with MDD who had a partial response or no response to selective serotonin reuptake inhibitors. A population of 75 patients were treated for 60 days with 15 mg L-methylfolate daily. The findings indicate that L-methylfolate was significantly more effective as compared with placebo. The response rates were 32.3% in the SSRI plus 15 mg L-methylfolate group compared with 14.6% in the SSRI plus placebo group. The number needed to treat to achieve response with the addition of 15 mg L-methylfolate to an SSRI was 6. Overall L-methylfolate was well tolerated with minimal adverse effects; manic symptoms developed in one patient in the L-methylfolate/SSRI group, which resulted in patient discontinuation.

A subset of the original acute treatment cohort was followed in a 12-month open-label continuation study during which outpatients were treated with 15 mg L-methylfolate and an SSRI. The researchers reported “high rates of response, remission, and recovery,” as well as overall safety, tolerability, and a good rate of retention.

Bipolar depression

Unfortunately, there is a paucity of research into the use of L-methylfolate to treat bipolar I depression (BD-I). To address this unmet need, Nierenberg and colleagues created an open label registry of patients with bipolar depression. The patients received treatment as usual as well as 15 mg L-methylfolate daily for 6 weeks. Pre-study medications included lithium, lamotrigine, quetiapine, valproate, lurasidone, levohydroxytride, and extended release methylphenidate. At week 6, there was a 50% or greater improvement on the Montgomery-Asberg Depression Rating Scale, with a pre-treatment mean score of 23.4 and a post-treatment score of 13.9 in six of the 10 patients studied. Significantly, the researchers noted that one patient had “an exacerbation in YMRS (Young Mania Rating Scale) and a possible manic episode.”

With that in mind, we present three case vignettes of women with affective disorders, two with MDD and one with BD-I. All three had acute symptoms of agitation shortly after augmenting their divergent psychotropic medication regimen with 15 mg of L-methylfolate. In all 3 cases, the agitation rapidly improved upon discontinuation of L-methylfolate.

Discussion

These case vignettes suggest that patients with unipolar or bipolar depression may be at risk for the onset of agitation shortly after beginning a trial of 15 mg L-methylfolate. In all three cases, the agitation resolved a few days after discontinuing the L-methylfolate, supporting the likelihood that it contributed to the agitation. It is interesting to note that the two patients with MDD both had a comorbid diagnosis of multiple sclerosis. This, however, may very well be coincidental.

The findings presented are preliminary and are presented with the aim of raising clinicians’ awareness that L-methylfolate may contribute to symptoms of agitation, irritability, and possibly hypomania, mixed mania, or mania in susceptible individuals. The only concrete conclusion that can be drawn is that well-designed clinical trials are needed to ferret out the rare but potentially significant adverse events associated with L-methylfolate.

There are no clinical data on the risks/benefits/adverse effects of the use of L-methylfolate off label in the treatment of bipolar depression. This is a significant lack of information, because many patients who ultimately have a diagnosis of bipolar disorder are initially treated—sometimes for years and even decades—for unipolar depression. The study by Papakostas and colleagues demonstrated that 7.5 mg of L-methylfolate performed no better than placebo as an augmentation agent in patients with MDD who did not respond to SSRIs, whereas 15 mg per day of L-methylfolate significantly separated from placebo. The dose response of L-methylfolate for effectiveness and adverse events in BD-I is unknown.

Future studies to assess the clinical consequences of augmenting antidepressants with L-methylfolate should include:

1. Large placebo controlled clinical trials of both unipolar depression and bipolar depression to determine the number needed to harm in the different patient populations, as

CASE VIGNETTE 1

“Jesse” was a 63-year-old married white woman who was on disability for multiple sclerosis. She struggled with treatment-resistant MDD for several years, with no evidence of a bipolar diathesis. She received numerous antidepressant medication trials, including therapeutic doses of phenelzine, fluoxetine, sertraline, norbuprtyline, escitalopram, mirtazapine, venlafaxine, vilaizodone, vortoxetine, and duloxetine; all of which failed. Pharmacogenomic testing of the MTHFR gene was consistent with decreased activity of this enzyme (C677T). It was decided to augment duloxetine with 15 mg L-methylfolate daily.

After several days on this regimen, her husband called to report that she had become uncharacteristically irritable and agitated. No identifiable situational stressors, substance use, new medication, or medical illness could be identified. Her long-term medical history was significant for multiple sclerosis, hypothyroidism, osteoporosis, neurogenic bladder, and hypertension.

Shortly after discontinuing the L-methylfolate, the irritability and agitation resolved. Upon obtaining further history, the patient reported a hypomanic-like adverse effect from previous prednisone treatment. There was no other history of bipolar spectrum symptoms.

CASE VIGNETTE 2

“Leslie” was a 43-year-old married white woman who presented with a history of treatment-resistant MDD with multiple antidepressant failures. The trials included imipramine, paroxetine, sertraline, escitalopram, duloxetine, venlafaxine, and fluoxetine. Her medical history was significant for multiple sclerosis, asthma, and migraines. She was taking venlafaxine XR 225 mg for an adequate duration, but there was a suboptimal response of her depressive symptoms when the 15 mg L-methylfolate daily was added. Upon follow-up six weeks later, she reported that her experience with the L-methylfolate was horrible, describing herself as feeling “agitated and aggressive.”

CASE VIGNETTE 3

“Susan” was a 56-year-old divorced white mother with a longstanding history of bipolar disorder who presented with an episode of depression. She had had previous episodes of mania, complicated mania with psychosis, and depression as well as several inpatient psychiatric hospitalizations for repeated manic episodes and psychotic symptoms; her most recent hospitalization was more than 15 years prior to the current episode of depression. Over the previous several years, her symptoms were reasonably well-managed on a combination of carbamazepine and oral/dano injection haloperidol. Chronic residual symptoms included a notably flat affect, anhedonia, and a largely depressed mood at baseline. Pharmacogenomic testing was performed as part of her work up, and it revealed that her MTHFR gene tested homozygous (T677T), which suggested poor enzymatic activity. A trial of 15 mg L-methylfolate daily was initiated to target recalcitrant depressive symptoms.

The patient called a few days after L-methylfolate initiation and described feeling unwell, agitated, and seeming to be a bit paranoid. She was instructed to discontinue the L-methylfolate, and these symptoms resolved within a few days. She reported that she quickly felt more like herself after discontinuing the L-methylfolate. She described the brief trial as horrible and stated that she “will never take it (L-methylfolate) again.”

L-Methylfolate

Continued from cover

Psychosomatics

MARCH 2020
well as the number needed to treat in bipolar patients.

2 Augmentation of non-SSRI antidepressants with L-methylfolate to determine if the improvement seen in MDD when SSRIs are augmented with L-methylfolate are generalizable to all antidepressants.

3 An evaluation of the L-methylfolate dosage range in patients with bipolar depression to determine which dosages (3.75 mg, 7.5 mg, 15 mg) are helpful and which are harmful.

These three cases illustrate the rare but possible adverse effects of agitation, irritability and possible onset of hypomania with adjunctive L-methylfolate. The publications reviewed report one patient who developed manic symptoms while taking L-methylfolate/SSRI for unipolar depression, and one patient who developed an increase in the YMRS and a possible manic episode when L-methylfolate was added to the regimen treating the underlying bipolar disorder. This activation by L-methylfolate is consistent with its putative mechanism of action, specifically increasing brain levels of norepinephrine, dopamine, and serotonin.

Conclusion

L-methylfolate, the bioactive form of folate that crosses the blood-brain barrier, has been shown to effectively augment SSRIs in patients with MDD who did not respond to SSRI monotherapy; and it also has shown to be generally well tolerated. Its role in augmentation in bipolar depression remains to be determined. Although the current data are limited, clinicians and patients should be aware of the possibility that L-methylfolate may increase agitation and may contribute to the onset of hypomania/mania.

Ms Robinson is Psychiatric-Mental Health Nurse Practitioner, Seacoast Mental Health Center, Portsmouth, NH; and Clinical Assistant Professor, Department of Nursing, University of New Hampshire, Durham. NPr, Dr Miller is Medical Director, Brain Health, Exeter, NH; Editor in Chief, Psychiatric Times; Staff Psychiatrist, Seacoast Mental Health Center, Exeter, NH; Consulting Psychiatric, Exeter Hospital, Exeter, NH; and Consulting Psychiatrist, Insight Meditation Society, Barre, MA. Ms. Robinson and Dr Miller indicate they have nothing to disclose regarding the subject of this article.

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“Among the new challenges is e-cigarette use by youths, which has skyrocketed to epidemic levels.”

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progression
Common Errors Psychiatrists Make When Managing Mood Disorders in Pregnant Patients

Jennifer L. Payne, MD

A 37-year-old woman with a history of recurrent major depression is currently stable on vonיצoxetine, a newer antidepressant. “Lauren” asks for advice regarding psychiatric medication use during pregnancy. She has a history of nonresponse to classic selective serotonin reuptake inhibitor medications and two psychiatric hospitalizations, one of which was after a serious suicide attempt. How should her psychiatrist advise her?

Managing psychiatric disorders in the setting of pregnancy is confusing and complex; complicating matters is a large amount of conflicting literature that is difficult to absorb, interpret, and use for best practices. Those of us who have specialized in perinatal psychiatry have spent a large amount of time thinking about the best approaches to designing treatment plans for pregnant patients. This article discusses a few common errors in the management of the perinatal psychiatric population (Table).

Stopping all medications
While medication discontinuation during pregnancy is appropriate for some patients, it is not for many others. Relapse rates for women with mood disorders who discontinue medications in pregnancy are incredibly high: up to 70% in women with major depression and 85% or higher for women with bipolar disorder.1,2 Many women suffer symptom relapse when their psychiatric medications are discontinued for pregnancy. In comparison, only one-third of women who do not stop their medications for pregnancy have symptom relapse. Thus, stopping medications practically guarantees that the pregnancy will be exposed to psychiatric illness.

Underestimating the risks
Psychiatric illness (especially depression) during pregnancy has been associated with multiple negative outcomes for the exposed baby, including preterm delivery, low birth weight, decreased motor tone and activity in the baby, higher cortisol levels in the baby, poor reflexes in the baby as well as overall worse health status and increased risk for preeclampsia and gestational diabetes. The negative effects of postpartum depression on exposed babies include lower IQ, slower language development, and higher rates of attention deficit-hyperactivity disorder as well as behavioral problems and psychiatric illness.

Exposure to maternal psychiatric illness either during pregnancy and/or during the postpartum period can lead to undesirable and negative outcomes for the exposed child. These risks should not be forgotten when considering whether to continue a psychiatric medication during pregnancy.

Under treating the illness
A second common scenario is that a woman’s medication is continued during pregnancy but at a lower dose than was needed to get her well. Or, conversely, the medication is continued but not increased or changed in the setting of illness recurrence. In this case, the woman and her baby are being exposed to both the medication and the psychiatric illness. The better approach is to treat to wellness—otherwise, why use the medication in the first place?

Switching
In general, perinatal psychiatrists recommend using older medications that we know more about in pregnancy rather than newer ones about which we know little to nothing in pregnancy. This rule of thumb applies to treatment planning before pregnancy. Once a woman is pregnant, the infant is already exposed to the newer medication and switching risks relapse of the illness as well as exposure to the second medication. So, if you are going to make change, do so before pregnancy.

Switching to a category B medication is similar to the previous error but it also involves a misunderstanding of the old FDA pregnancy category B. The old pregnancy categories are being phased out and replaced with a summary on the label of all available data on the safety and risks of a medication during pregnancy and lactation. However, the pregnancy categories are still used for some older medications and are readily available on the internet.

Category B combines medications that have reassuring animal data but no human data, with medications that have demonstrated an adverse effect in animals but have no demonstrated risk in humans. Thus, many providers conclude that if a medication is category B, the medication is safer to use during pregnancy compared with a category C or D medication. However, many Category B classified medications simply have no human data at all and therefore are not preferable over medications that we have safety and risk data for in humans.

Switching to a different medication while breastfeeding because it has a lower passage into breast milk is a well-intentioned practice but also increases the number of exposures for the
infant: to the medication used during pregnancy (note that the exposure in utero is far larger than the exposure in breastfeeding) to the medication used in breastfeeding, and potentially to psychiatric relapse. Switching to a different medication while breastfeeding should only be done in the case of a history of response to medication that could not be used during pregnancy but can be used during breastfeeding (such as valproic acid) or in the case of taking a medication during pregnancy that should not be used during breastfeeding, such as clozapine and in some cases lithium. A switch can also be made if there is symptom relapse on the current psychiatric medication(s) but not for the purposes of limiting exposure during breastfeeding.

Switching prior to pregnancy

It often makes sense to try to “clean up” a medication regimen and switch to medications with more data prior to pregnancy. However, when a woman is older, her risk of genetic malformations increases with each passing year. In the spirit of treating the whole patient, taking time to change a medication regimen and risk relapse and spend time finding a medication regimen that is helpful may not make sense. In this setting, the provider does best to educate the patient about this risk to make sure she makes an informed decision about her treatment options.

Stopping benzodiazepines

Many clinicians get nervous about benzodiazepine use in pregnancy and, particularly in the setting of an unplanned pregnancy, will refuse to prescribe benzodiazepines when a woman finds herself pregnant. However, sudden discontinuation of benzodiazepines can precipitate withdrawal symptoms including unstable changes in blood pressure and heart rate, and can result in seizures, none of which are particularly good for the patient, her baby, or the pregnancy.

Attempting to taper and minimize the regular use of benzodiazepines during pregnancy is a more reasonable approach that supports the health of both mother and baby. Tapering of benzodiazepines can be accomplished by switching to a longer-acting agent followed by a taper of 20% every 24 hours in the setting of a motivated patient and good supports. Many patients will require a slower taper and can be decreased every 3 to 7 days.

Ignoring substance use

I have evaluated a number of patients concerned about their psychiatric medications in pregnancy yet they continue to smoke tobacco, drink alcohol, use marijuana, or take opiates. It is important to address these known risk factors for negative pregnancy outcomes and emphasize that these substances have very clear risks if continued during pregnancy. In comparison, most (but not all) psychiatric medications do not.

Antipsychotic use

I have evaluated a number of patients in which appropriate treatment has been withheld because the patient was pregnant. Providers have the good intention of not exposing the baby to psychiatric medications; however, they neglect the very real risk of exposure to psychiatric illness and unhealthy and unpredictable maternal behaviors. Furthermore, there are very few medical illnesses for which we withhold treatment during pregnancy and psychiatric illness should not be an exception.

Lithium

Unfortunately, lithium use during pregnancy has a very bad reputation because of early studies that found an increased rate of Ebstein anomaly in utero exposed infants. However, more recent data reveal that the risk of Ebstein anomaly in exposed infants is less than 1%, while the risk of relapse of bipolar I disorder with discontinuation of lithium during pregnancy is approximately 85% to 100%. Lithium should be considered as a possible treatment option during pregnancy for patients who respond well to lithium and have a history of severe bipolar illness. You also may want to consider switching to an atypical antipsychotic although this carries a risk of relapse in patients who respond to lithium.

Lithium use during breast-feeding remains controversial. Although it can be supported in some individual cases, it is not recommended in patients who are disorganized or unlikely to recognize dehydration in an infant.

Valproic acid, carbamazepine

To be clear, I am not recommending that valproic acid or carbamazepine not be prescribed to women who may become pregnant. I am, however, recommending that contingency plans be in place when these medications are prescribed in women because neither should be used in pregnancy except in exceptional circumstances. If valproic acid or carbamazepine are to be used in a woman who has the potential to become pregnant, it is important that she clearly understands that she should not take these medications during pregnancy and that any pregnancy should be a planned one, and other medications will be used during pregnancy.

Discussion of contraception choices should be carried out and initiation of contraception should be encouraged and if possible undertaken. In addition, the association between valproic acid exposure and the development of polycystic ovarian syndrome as well as the potential for decreased fertility should be discussed with the patient.

In general, I recommend prescribing valproic acid and carbamazepine in women of reproductive age only when other, safer medication choices for pregnancy such as lithium or atypical antipsychotics have failed.

Discussion

Let’s return to the clinical case described at the beginning of this article. What are some appropriate treatment options for Lauren during pregnancy?

She has a history of severe illness requiring hospitalization, a history of a significant suicide attempt, and a history of non-response to SSRI medications. She is, however, on a newer antidepressant about which we know little during pregnancy.

One option is to attempt to switch her to an older medication about which we know more, as long as it is not an SSRI since she has a history of nonresponse.

However, since Lauren is in her late 30s it might not make sense to take the time to undertake medication trials and risk relapse of her illness, which has been severe in the past. Her options should be discussed in detail, using a risk-risk approach: discussing the risks of psychiatric medication use during pregnancy, the risks of switching to a different medication, and the risks of psychiatric illness during pregnancy to both the patient, her pregnancy, and her infant.

Finally, let’s revisit her case with the added detail that Lauren is, in fact, currently pregnant. Does this change recommendations? Absolutely. If Lauren is already pregnant, it does not make sense to switch to an older medication because the developing baby is already exposed to the medication and switching increases the risk of relapse and exposing the baby not only to the original antidepressant but also a second medication. In this case, it would be better to continue with a medication known to work for Lauren and try to minimize the number of exposures for the baby.

There are no easy answers in designing a psychiatric medication plan for pregnancy, but a calm, thoughtful approach can help us promote maternal mental health which is not only good for the mother, but also for her baby.

Dr Payne is Associate Professor of Psychiatry, Associate Professor of Gynecology and Obstetrics, Director, Johns Hopkins Women’s Mood Disorders Center, Johns Hopkins School of Medicine, Baltimore, MD. She reports no conflicts of interest concerning the subject matter of this article.

REFERENCES

Managing Behavioral and Psychological Symptoms of Dementia

> Rajesh R. Tampi, MD, MS, and Deena J. Tampi, MSN, MBA-HCA

Alzheimer disease (AD) and other dementias are a major and increasing global health challenge. In 2010 there were 35.6 million individuals with dementia; these numbers are expected to double every 20 years and reach approximately 115.4 million by 2050.

Behavioral and psychological symptoms of dementia (BPSD) is used to describe a group of diverse non-cognitive symptoms and behaviors that are frequently seen among individuals with dementia. BPSD affects approximately 90% of individuals at some point during the course of the illness, with greater prevalence noted among individuals receiving skilled care.

Common BPSD include apathy, anxiety, depression, agitation, psychosis, sleep disturbances, dysphoria, aberrant motor activity, hallucinations, and delusions. There is emerging evidence that specific symptom patterns can be identified in different types of dementias. One recent study found that hallucination, abnormal motor behavior, and anxiety were significantly more frequent in Alzheimer disease and mixed dementia (MD) compared with vascular dementia (VD). Hallucinations and delusions were significantly more severe in AD and MD. Disinhibition was significantly more frequent and severe, and agitation was significantly more severe, in patients with VD.

BPSD is associated with faster cognitive decline, greater functional impairment, and reduced quality of life for patients and their caregivers. BPSD is also a risk factor for earlier institutionalization among individuals with dementia. Moreover, BPSD adds to the overall cost of caring for individuals with dementia.

This spectrum of symptoms is thought to occur due to the complex interaction between biological, psychological, social, and environmental factors. These factors include structural, functional, and neurochemical changes in the brain, underlying medical or psychiatric disorders, preexisting personality traits, caregiver distress/depression, and misleading or lack of stimuli from the environment.

**Assessment**

When an individual is being assessed for BPSD, it is vitally important to collect information from the caregivers of these individuals. Collateral information will provide insight into the type and duration of symptoms, aggravating and mitigating factors, prognostic factors, and a history of interventions that have been beneficial in managing BPSD. Underlying medical and psychiatric conditions should be evaluated and appropriately managed, as they might be precipitating and/or worsening the BPSD. A thorough medication review will help eliminate the effect of medications, which may cause and/or aggravate the BPSD. This is also true of any illicit substances.

An assessment of BPSD includes antidepresants, antipsychotics, anticonvulsants, and cholinesterase inhibitors.

**Management**

Both nonpharmacological and pharmacological management strategies have been found to be beneficial among individuals with BPSD.

Among the nonpharmacological strategies, music therapy and behavioral management techniques appear to be effective for reducing the BPSD. These interventions have been shown to reduce the frequency and severity of the BPSD and also decrease caregiver burden with effect sizes similar to those of associated with pharmacotherapy.

To be successful, nonpharmacological interventions need to be individualized and delivered in a caring way in a caring environment. Nonpharmacological interventions that target both the patient and the caretaker improves the lives of both partners in the dyad.

Nonpharmacological management strategies are often used prior to or in conjunction with pharmacotherapy. This is done to minimize the exposure of individuals with BPSD to pharmacotherapeutic agents, given their significant adverse effect profile.

Although there are no FDA-approved medication classes to manage BPSD, many medications have been tested. Common medication classes that have been used in the management of BPSD include antidepresants, antipsychotics, anticonvulsants, and cholinesterase inhibitors.

Findings from a meta-analysis indicate that only two medications had statistically significant higher response rates than placebo in the management of BPSD.

**Table. Improved outcomes with aripiprazole, quetiapine, and risperidone compared with placebo**

<table>
<thead>
<tr>
<th>Rating scale</th>
<th>Standardized mean difference</th>
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<tbody>
<tr>
<td>Aripiprazole</td>
<td></td>
</tr>
<tr>
<td>NPI</td>
<td>-0.17</td>
</tr>
<tr>
<td>BPRS</td>
<td>-0.20</td>
</tr>
<tr>
<td>CMAI</td>
<td>-0.30</td>
</tr>
<tr>
<td>Quetiapine</td>
<td></td>
</tr>
<tr>
<td>BPRS</td>
<td>-0.24</td>
</tr>
<tr>
<td>Risperidone</td>
<td>-0.26</td>
</tr>
</tbody>
</table>

NPI, Neuropsychiatric Inventory; BPRS, Brief Psychiatric Rating Scale; CMAI, Cohen-Mansfield Agitation Inventory.

**“Findings from a meta-analysis indicate that only two medications had statistically significant higher response rates than placebo in the management of BPSD.”**
American Psychiatric Association (APA) Practice Guideline Recommendations for Managing BPSD

1. A risk and benefit analysis should be completed before prescribing antipsychotics to individuals with BPSD.
2. If the analysis favors the use of antipsychotics, then treatment should be initiated at the lowest possible dose and titrated to the minimum effective dose as tolerated.
3. If clinically significant adverse effects occur from the use of an antipsychotic, the potential risks versus benefits of using the medication should be reevaluated.
4. If the use of the medication does not provide any appreciable benefit after a 4-week trial at an adequate dose, then the medication should be tapered and discontinued.
5. If there is good response from the use of the antipsychotic, unless there are contraindications, an attempt to taper and withdraw the medication should be made within 4 months of initiation of treatment, after discussions with the individual and his or her caregiver.
6. When the medication is being tapered, the patient should be evaluated monthly for at least 4 months after the medication has been discontinued.
7. In the absence of delirium, haloperidol should not be used as a first-line agent for management of BPSD.
8. Individuals with BPSD should not receive long-acting injectable antipsychotics, unless they have a co-occurring chronic psychotic illness.

REFERENCES


Neuropsychiatry

College of Medicine, Case Western Reserve University, Cleveland, OH; Ms. Tampi is Executive Vice President, Diamond Healthcare, Richmond, VA. The authors report no conflicts of interest concerning the subject matter of this article.

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- Learn about how new therapies work to treat various psychiatric conditions
- Get a better understanding of the impact of psychiatric disorders for those affected
- Explore future directions for treating psychiatric disorders
- Earn CE credit while interacting with psychiatric experts and peers

**Agenda:**

**Thursday, October 15, 2020**

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
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<tr>
<td>12:00</td>
<td>Registration and Lunch</td>
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<tr>
<td>1:00</td>
<td>Sleep, Migraine, Psycho-Oncology</td>
</tr>
<tr>
<td>1:15</td>
<td>Interventions for Sleep Disturbances in Psychiatric Disorders</td>
</tr>
<tr>
<td>1:30</td>
<td>The Interplay of Migraines and Psychiatric Disorders: Treatment Implications</td>
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<tr>
<td>1:45</td>
<td>Panel Discussion, Q&amp;A</td>
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<tr>
<td>2:15</td>
<td>Clinical Psycho-Oncology: Assessment and Management</td>
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<tr>
<td>2:30</td>
<td>BREAK</td>
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<tr>
<td>3:00</td>
<td>Hot Topics</td>
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<tr>
<td>3:15</td>
<td>Cannabis in Psychiatry: Clinical, Legal, and Ethical Issues</td>
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<tr>
<td>3:30</td>
<td>The New Role of Psychotics</td>
</tr>
<tr>
<td>3:45</td>
<td>Panel Discussion, Q&amp;A</td>
</tr>
<tr>
<td>4:00</td>
<td>Special Lectures, Giants in Psychiatry</td>
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<tr>
<td>4:15</td>
<td>Diagnosing and Treating PTSD</td>
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<tr>
<td>4:30</td>
<td>Special Guest Speaker</td>
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<tr>
<td>5:00</td>
<td>ADJOURN</td>
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<tr>
<td>5:00</td>
<td>Welcome Reception</td>
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</table>

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- Hear about strategies for early diagnosis and intervention to improve outcomes
- Learn about how new therapies work to treat various psychiatric conditions
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- Explore future directions for treating psychiatric disorders
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<tbody>
<tr>
<td>7:00 am</td>
<td>Registration and Breakfast</td>
</tr>
<tr>
<td>8:00 am</td>
<td>Welcome, Introductions, and Presession Questions</td>
</tr>
<tr>
<td><strong>Plenary Session: Special Report on Major Depressive Disorder</strong>&lt;br&gt;8:10 am</td>
<td>Diagnostic Issues in Mood Disorders</td>
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<tr>
<td>8:35 am</td>
<td>State-of-the-Art Treatment in Major Depressive Disorder</td>
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<tr>
<td>9:00 am</td>
<td>Treatment-Resistant Depression</td>
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<tr>
<td>9:15 am</td>
<td>Treating Major Depressive Disorder: Beyond MAOIs and SSRIs</td>
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<tr>
<td>9:30 am</td>
<td>BREAK</td>
</tr>
<tr>
<td><strong>Plenary Session: Special Report on Bipolar Disorder</strong>&lt;br&gt;10:00 am</td>
<td>State-of-the-Art Treatment in Bipolar Disorder</td>
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<tr>
<td>10:30 am</td>
<td>Medical Crossfire®: Should Bipolar Depression be Treated With Antidepressants?</td>
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<tr>
<td>10:45 am</td>
<td>Combination Therapy in Bipolar Disorder</td>
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<tr>
<td>11:00 am</td>
<td>Maintenance Therapy in Bipolar Disorder</td>
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<tr>
<td>11:15 am</td>
<td>Postsession Questions</td>
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<tr>
<td>11:20 am</td>
<td>Keynote Lecture</td>
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<td>12:00 pm</td>
<td>Non-CME Lunch</td>
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<tr>
<td><strong>Specialist Track: Clinical Conundrums and Commentary</strong>&lt;br&gt;1:30 pm</td>
<td>Major Depressive Disorder</td>
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<td>2:15 pm</td>
<td>Bipolar Disorder</td>
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<tr>
<td><strong>Primary Care Track</strong>&lt;br&gt;1:30 pm</td>
<td>Treating Major Depressive Disorder in a Primary Care Setting</td>
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<tr>
<td>2:00 pm</td>
<td>Treating Anxiety in a Primary Care Setting</td>
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<tr>
<td>2:30 pm</td>
<td>Panel Discussion, Audience Q&amp;A</td>
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<tr>
<td>3:00 pm</td>
<td>BREAK</td>
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<tr>
<td><strong>Plenary Session: Hot Topics</strong>&lt;br&gt;3:30 pm</td>
<td>Presession Questions</td>
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<tr>
<td>3:45 pm</td>
<td>Treatment Strategies for Attention-Deficit/Hyperactivity Disorder</td>
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<tr>
<td>3:55 pm</td>
<td>Psychosocial, Causes, and Treatment of Binge Eating Disorder</td>
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<tr>
<td><strong>Plenary Session: Special Report on Psychiatry and Women's Health</strong>&lt;br&gt;4:05 pm</td>
<td>Practical Psychoneuroendocrinology: How the Brain, Nervous System, and Endocrine System Interact</td>
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<tr>
<td>4:25 pm</td>
<td>Psychosocial and Psychopharmacological Options for Postpartum Depression</td>
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<tr>
<td>4:40 pm</td>
<td>Effective Strategies for Hypoactive Sexual Desire Disorder</td>
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<td>4:55 pm</td>
<td>Postsession Questions</td>
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<td>5:00 pm</td>
<td>ADJOURN</td>
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<td>RECEPTION</td>
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**Saturday, October 17, 2020**

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<tr>
<td><strong>Plenary Session: Special Report on Substance Abuse</strong>&lt;br&gt;8:16 am</td>
<td>Treatment for Opioid Use Disorder</td>
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<tr>
<td>8:40 am</td>
<td>Medication-Assisted Treatment and Alternative Therapies for Addressing Addiction</td>
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<tr>
<td>9:05 am</td>
<td>Methamphetamine Abuse and Treatment Options</td>
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<tr>
<td>9:20 am</td>
<td>Medical Crossfire®: Should Benzodiazepines and Opioids Be Used Concurrently?</td>
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<tr>
<td>9:35 am</td>
<td>Audience Q&amp;A</td>
</tr>
<tr>
<td>9:45 am</td>
<td>BREAK</td>
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<tr>
<td><strong>Plenary Session: Special Report on Schizophrenia</strong>&lt;br&gt;10:15 am</td>
<td>Diagnosing Schizophrenia</td>
</tr>
<tr>
<td>10:35 am</td>
<td>State-of-the-Art Treatment in Schizophrenia</td>
</tr>
<tr>
<td>10:55 am</td>
<td>Long-Acting Injectables for Schizophrenia</td>
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<td>Practical Strategies for Addressing Sleep Disorders</td>
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<td><strong>Hot Topics: Overcoming Challenges Associated With Antipsychotics</strong>&lt;br&gt;3:30 pm</td>
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The Coercive Cycle: A School to Prison Pipeline?

Marc S. Atkins, PhD, and Angela L. Walden, PhD

The report, Illinois issued new guidelines. Despite federal law. In this article, we discuss the reasons for the maintenance of abusive disciplinary practices with youth despite considerable evidence for more effective alternatives, suggest a renewed focus on reducing disparities and promoting equitable funding across communities, and share thoughts and implications for psychiatrists.

Seclusion from peers and adults, has long been considered controversial. Seclusion is banned in four states and fractions. As noted in the report, seclusion has been associated with negative physical and psychological outcomes, including death, and children with disabilities and mental health needs are at increased risk for seclusion relative to their peers. This past November, the Chicago Tribune in collaboration with ProPublica, published a report on the use of seclusion for children and youth in schools and special education settings across Illinois. The report revealed shocking abusive practices, including long-duration seclusions for young children, lack of adult oversight, and overly harsh discipline for minor infractions. As noted in the report, seclusion is banned in four states and restricted in sixteen others. Following the report, Illinois issued new guidelines and now bans this practice.

More recently, a group of Illinois congressional representatives issued a letter to the Secretary of Education asking her to ban all seclusions in educational settings nationwide. As noted in these reports and letters, there is no therapeutic rationale for long-duration seclusion, and there are many more viable and effective alternatives. Moreover, findings indicate that abusive disciplinary practices in schools are disproportionately applied to youth of color with significant disruption in their learning; often referred to as the school-to-prison pipeline.

According to the recent collaborative report from the Chicago Tribune and ProPublica, only 19 states have banned school seclusion, and such practices are not regulated by federal law. In this article, we discuss the reasons for the maintenance of abusive disciplinary practices with youth despite considerable evidence for more effective alternatives, suggest a renewed focus on reducing disparities and promoting equitable funding across communities, and share thoughts and implications for psychiatrists.

**Harsh discipline**

Harsh discipline with children—whether it is corporal punishment by parents or overly punitive practices in schools—has long been established as ineffective and counter-productive, yet it remains a common practice. Harsh disciplinary practices lead to high rates of childhood aggression and delinquency, with strong intergenerational transmission. Gerald Patterson, PhD, and colleagues at the Oregon Social Learning Institute first identified what they termed coercive family processes: escalating child misbehavior is met with escalating punitive practices by parents. They noted that the adult overuse of punishment is often a model for the child to use aggression to solve problems with peers or teachers. Their research led to the development of a generation of programs to teach parents and teachers alternative discipline practices. The coercive cycle Several decades of experience in urban schools in Philadelphia and Chicago provided our research team with more than enough anecdotal evidence that the coercive cycle was a well-established pattern, but empirical data were lacking to document the nature and extent of disciplinary practices. In collaboration with a principal at one Chicago Public School in which we were consulting, we collected and catalogued disciplinary records for all 3rd through 8th grade students (N = 314) for an entire school year.

We found that the coercive cycle was in place for some but not all students. Specifically, being disciplined was a deterrent for about 20% of students; after being disciplined in the fall, they did not receive any other discipline for the rest of the school year. Instead, the findings were more troubling. Their infractions were more serious (e.g., fighting, cursing) and the punishment more severe (expulsion rather than detention). Of even more concern, being disciplined led to increased disruptive behavior throughout the school year. As a group, these students were rated as highly aggressive by teachers and were less popular with their peers. Based on the escalation of their disruptive behavior, the consequences appeared to serve as a reward rather than a punishment. That is, for these students, being removed from the classroom may have been preferred over remaining in a classroom, which was supposed to be a negative experience for them. Teachers were also relieved with the removal of disruptive students from the classroom, because it allowed them to resume their teaching. Thus, for these students, the coercive cycle was fully entrenched (Figure).

Children with autism spectrum disorder comorbid with ADHD had...
especially high rates of harsh discipline. Reducing the use of parental harsh discipline was found to be especially important for preschool children with ADHD through reduced autonomic responding associated with anger management and emotional behaviors. A recent study of disciplinary practices in high schools and middle schools in Maryland noted high rates of suspension for students with disabilities. This was especially pronounced in low-achieving schools serving students in areas of lower socioeconomic status.

Funding and resources
The processes supporting the coercive cycle are well established behavioral patterns that can be difficult to modify, and the stakes in psychiatric and special education facilities are even higher. In fact, following the ProPublica and Chicago Tribune report, the Illinois State Department of Education issued a statewide ban on seclusion in child psychiatric facilities only to lift the ban in favor of increased monitoring after programs indicated that without these procedures they would need to discharge their most aggressive youth. Clearly, the state was unprepared to accommodate these facilities to fully address the needs of these youth.

From a psychiatric public health perspective, this report and the subsequent responses highlight the urgent need to address the poor state of public education for our most vulnerable youth. It is understandable that legislators and advocates are looking to government officials to ban abusive practices, such as seclusion, but a focus only on what not to do will likely only push this problem further underground. It is not a lack of knowledge that is perpetuating these abusive practices, but a lack of willingness to fund programs, and staff, at levels needed to assure effective practices.

Some three decades ago, our research team consulted at a large state psychiatric hospital outside of Philadelphia and saw first-hand how staff shortages and lack of training led to abusive disciplinary practices. Young patients and patients of color were most likely to receive long seclusions, lasting between four and 5 hours—and the staff were unprepared for the more complex behavioral reward programs we recommended, such as increased

To read “The Quiet Rooms” published by ProPublica and the Chicago Tribune, go to https://graphics.chicagotribune.com/illinois-seclusion/index.html. Share your comments on this article and other pieces by emailing PTEditor@mmhgroup.com.

Kenneth J. Weiss, MD  ||  For the Group for the Advancement of Psychiatry Committee on Arts & Humanities

Across the centuries, March has been an eventful month for the insanity defense on both sides of the Atlantic, and the McNaughten rule remains the prevalent standard to this day.

On March 2, 1843, Daniel McNaughten went on trial for murder, leading to a ruling of not guilty by reason of insanity. The McNaughten Rule has influenced insanity defenses ever since.

In the 1840s, Britain was the scene of protests over the Corn Laws, which stressed lower socioeconomic classes by taxing grain. Prime Minister Robert Peel of the Tory Party was vilified as an oppressor. A Scottish woodworker, McNaughten, became obsessed with Peel, believing he and the Tories were persecuting him, directly and severely enough to threaten his life. Under that fixed idea in 1843, he came to London to study and assassinate Peel in order to save his own life.

On January 20, 1843, McNaughten lay in wait near Peel’s home. A man left the home, and McNaughten shot him from behind. The victim, however, was not Peel; rather, it was his secretary, Edward Drummond. Though it remains controversial whether McNaughten knew he was shooting the wrong man,1 sources say the shooter believed he had shot Peel.2 Regardless, the shooting was intentional. The victim died less than a week later, making it a murder case.

On March 2, 1843, McNaughten’s trial began at the Central Criminal Court of London. He had a talented lawyer, Alexander Cockburn. Expert testimony said that as a result of his delusions, McNaughten did not know what he was doing was wrong. Cockburn, who had read A Treatise on the Medical Jurisprudence of Insanity published in 1838 by American physician Isaac Ray, relied on Ray’s idea that there should not be a single test for insanity. The defense so persuaded Lord Chief Justice Tindal that he directed a verdict of not guilty on the ground of insanity. McNaughten, considered dangerous, was civilly committed, the custom that began in 1800.1

The verdict did not sit well with Queen Victoria, who had been the object of threats and attempts to harm her. She was incredulous that a man who opposed the conservative government would be considered insane and not responsible. The House of Lords promptly held an inquiry asking legal experts a series of questions. For example: What is the proper test for criminal responsibility?

The consensus was that the correct test is whether the defendant, at the time of the act, labored under such a defect of reason from disease of the mind as not to know the nature and quality of the act he was doing, or as not to know what he was doing was wrong.2 This was a cognitive test (knowing right from wrong), in contrast to the volitional test (not having the will to resist an impulse). The new standard became known as the McNaughten Rule, even though McNaughten was not tried under it. It quickly caught on in America, where it remains the predominant standard for insanity.

In the mid-20th century, Dr. Ray’s advice was evident. First, federal jurisdiction in 1954 permitted juries to consider a standard Ray supported in 19th century: “an accused is not criminally responsible if his unlawful act was the product of mental disease or mental defect.” Then, in 1972, the federal jurisdiction adopted the American Law Institute’s standard (a volitional test in addition to a cognitive test).3

On March 30, 1981, John Hinckley Jr shot and wounded President Reagan and his press secretary, James Brady. He was tried and acquitted by reason of insanity under the federal standard. This troubled Congress, just as it did the Crown after the Drummond assassination. The result was the removal of the volitional standard in new legislation—the Insanity Defense Reform Act of 1984—and a return to the McNaughten Rule.4

REFERENCES


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Treatment Nonadherence
An Epidemic Hidden in Plain Sight

Mansoor Malik, MD, Suneeta Kumari, MD, and Partam Manalai, MD

The impact of nonadherence is staggering. It is estimated that at least 50% of patients with chronic health conditions are nonadherent; similarly, 20% to 30% of prescriptions are not even filled. In the US, nonadherence is responsible for an estimated 125,000 deaths and between $100 to $300 billion in medical costs annually.

Treatment nonadherence in patients with psychiatric disorders is similar or higher than with other chronic conditions. At least 61% of patients with schizophrenia, 57% of patients with bipolar disorder, and 52% of patients with depression have problems with adherence. Even with depot medications, many patients are treatment nonadherent within one year.

Measurement of adherence
Measuring adherence is tricky. Adherence to treatment occurs on a spectrum from total adherence to total nonadherence. It is also a dynamic process—patients can be selective in their adherence, and their adherence levels can change over time. The definition of adherence also varies: nonadherence is defined as patients missing medications from 20% to 50% of the time.

Adherence is almost always overestimated. Most studies use pharmacy prescription claims data as a proxy for adherence. Most commonly used are Medication Possession Ratio (MPR) and the Proportion of Days Covered (PDC). MPR is the ratio of the number of days for which a patient has medications on hand divided by the total number of days the patient was observed. Because the assumption is that nonadherent patients are unlikely to fill their prescriptions, MPR is likely to overestimate adherence for patients who fill their prescriptions. The Proportion of Days Covered (PDC) can be more accurate. It uses several covered days for which patients have medications on hand. However, neither MRP nor PDC measure actual ingestion of medications.

Technology-based solutions are available that can closely approximate patients’ adherence. The Medication Event Monitoring System (MEMS) uses microtechnology to detect when a medication container is opened. This technology can be applied to smart pillboxes labeled with the day and time of each medication. The data are transferred via the patient’s cell phone to providers. MEMS can also send text messages to remind patients to take their medications.

Another approach is edible digital sensors embedded in the medication. The sensors are activated by gastric acid and send a signal to a remote monitoring system. In 2018, the FDA approved the first use of this technology for mental health disorders. A tablet formulation of aripiprazole was approved with a small (1 mm x 1 mm) sensor. Activated in the stomach it sends a signal to a wearable sensor worn on the chest. The data are then transmitted to a cloud server via a smartphone app, and can be accessed by the treating clinician.

Factors affecting adherence
Multiple factors play a role in nonadherence (Table 1); most is attributable to patients’ perceptual factors. Findings from a cross-sectional study of patients with chronic health conditions indicate that 62% of patients forgot to take their medications, 37% reported running out of medications, and 23% were careless about taking medications.

Three themes of medication adherence came to light in a review of the literature on schizophrenia: perceived lack of control, risk of dependence on medications or provider, and stigma associated with medication use. Self-efficacy and an internal locus of control are positively correlated with medication adherence. While poor insight into illness is associated with higher rates of previous admissions and nonadherence.

Another predictor of adherence is physician-related—the therapeutic alliance plays a key role in treatment adherence. A collaborative relationship, agreement on treatment tasks, and stability of the alliance are necessary elements of better treatment adherence. The patient needs to be involved in the decision-making process for treatment because factors such as medication dosage, pill burden, and regimen complexity influence adherence. Practical and financial issues also affect adherence: how difficult is it for the patient to get to appointments or pharmacies for prescriptions? Can the patient afford the copays for medications? An analysis of comprehensive Medicaid claims shows that the increase in medication copayment is directly related to nonadherence.

As expected, stigma and perceived discrimination about mental health issues can have a negative impact on adherence. In a large study, self-stigma highly correlated with rates of nonadherence; patients with bipolar disorder had the highest rates of medication discontinuation at 65%, but living with a partner lowered the rates of self-stigma and decreased nonadherence. Symptom severity and overall level of disability also negatively correlated with adherence.
Interventions delivered by nurses and pharmacists had better results than those provided by physicians.

There are an estimated 300 million cell phones in the US, and most of the people use text messaging. Text messaging has been one of the most common interventions used to enhance adherence. A systematic review found that reminders such as phone calls were most effective.2

Conclusion
Treatment nonadherence is highly prevalent with significant negative consequences, yet it is rarely addressed in routine clinical care. A high index of suspicion is needed to identify nonadherence and when identified, use evidence-based interventions address nonadherence.

Nonadherence should be addressed at multiple levels. Recent technological advances have made it possible to leverage mobile communication to improve adherence; however, a great need still exists for adequately powered studies to elucidate the mechanisms of and interventions for treatment nonadherence.

Dr Malik is Clinical Professor, Johns Hopkins University, Baltimore, MD; Dr Kumar is Research Assistant, and Dr Manalai is Associate Professor, Howard University Hospital, Washington, DC. The authors report no conflicts of interest concerning the subject matter of this article.

REFERENCES

Table 2. Examples of adherence interventions

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<tr>
<th>Category</th>
<th>Example</th>
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<tbody>
<tr>
<td>Educational</td>
<td>Change illness beliefs, psychoeducation about illness/medications, follow up by nurses/pharmacists</td>
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<tr>
<td>Behavioral</td>
<td>Memory aids such as pill boxes and blister packs, behavioral cueing, reminder calls/texts</td>
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<td>Medication regimen</td>
<td>Elimination of unnecessary medications, once daily doses, use of extended release and depot medication, addressing medication adverse effects, 90-day medication supply</td>
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<td>Integrated care</td>
<td>Physician access to pharmacy fill data, accurate medication reconciliation, frequent and regular appointment, case management</td>
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<tr>
<td>Financial</td>
<td>Lowering/elimination of pharmacy copayments, contingency management</td>
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<tr>
<td>Social</td>
<td>Involvement of family and/or caregivers, promotion of self-reliance, improved access to care and/or community supports</td>
</tr>
<tr>
<td>Technological</td>
<td>Digital health technologies, medication event monitoring system</td>
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"Interventions delivered by nurses and pharmacists had better results than those provided by physicians."
Chaos Theory With a Human Face
Niall McLaren, MBBS, FRANZCP

Dr Niall McLaren is an Australian psychiatrist with a rich clinical experience of practicing psychiatry with limited resources in some of the most remote parts of the English-speaking world. He has a lifelong interest in the philosophical and logical status of theories used in psychiatry. He is the author of a trilogy of books (Humanizing Madness, Humanizing Psychiatry, and Humanizing Psychiatrists) in which he takes on the task of developing a biocognitive model of mind and mental illness, which he sees as a replacement for the 19th century ideologies of psychoanalysis, behaviorism, and biological psychiatry. His most recent publication is Anxiety: The Inside Story.

Dr McLaren has long argued that psychiatry lacks a formal model or theory of mental disorder and that the current practice of psychiatry lacks scientific standing. He has criticized the ethos of biological reductionism, which sees mental disorders as brain disorders. While he is an acerbic critic of mainstream psychiatry, his criticisms are driven by a passionate desire to see psychiatry evolve into a philosophically and scientifically mature discipline. Largely ignored by mainstream psychiatry, his critical writings have amassed a significant worldwide readership. I may disagree with his views, but it is my fervent belief that psychiatry has much to gain by engaging with thoughtful critics like Dr McLaren.

Awais Aftab, MD

There is a great deal that ails psychiatry—over-diagnosis, over-treatment, misallocation of resources, consistent breaches of patients’ fundamental human rights, and so forth—and they all go back to the one problem: mainstream psychiatry lacks a scientific framework. It is not a science because it does not have an articulated, publicly available model of its field capable of generating testable predictions. Everybody thinks there is a model, called the biological or medical model of mental disorder, but it does not exist. It is like the phantom biopsychosocial model attributed to George Engel: He argued for the need for such a model, but he did not actually present one. Everybody thinks he did, he talked as though he did, but he didn’t. A model needs to be set out as a series of internally consistent propositions that generate an empirical research program. Psychiatry does not have one, because we do not have a concept of the nature of mental disorder. This is not just our fault; it derives from the larger philosophical problem that there is not an accepted model of normal mind. When the psychoanalytic or psychodynamic models of mind were shown to be non-scientific, psychiatry retreated to the biological corner thinking it could save us, but nobody has ever shown that we can explain the mind in brain terms. Nor will they ever do it.

AFTAB: Earlier in your career, while you worked in the remote Kimberley Region of Western Australia for six years, you may have been the world’s most isolated psychiatrist. Did that experience have any bearing on your subsequent approach to psychiatry? It certainly fits in with your highly original ideas, and your intellectual journal appears to have been a largely isolated one as well.

There is a great deal that ails psychiatry—over-diagnosis, over-treatment, misallocation of resources, consistent breaches of patients’ fundamental human rights, and so forth.

AFTAB: You have commented on how the current practice of psychiatry tends to ignore personality disorders, and the notion of personality dysfunction as a cause of psychiatric syndromes (former axis I) such as major depression is largely discounted. This is consistent with my clinical experience as well. For instance, psychiatry recognizes that individuals with personality disorders are more likely to have treatment resistant depression, yet the treatment algorithms for treatment resistant depression do not really take that into account. And, in practice, that leads to aggressive pharmacotherapy. Does this help explain why treatment resistance appears to be the rule rather than the exception in clinical settings?

PART 1

There is a great deal that ails psychiatry—over-diagnosis, over-treatment, misallocation of resources, consistent breaches of patients’ fundamental human rights, and so forth.

MCLAREN: Part of the reason I left Perth to go north was because of the covert hostility of the psychiatric establishment in that very isolated city to anything that questioned what they were doing. I had enrolled in a PhD jointly with the department of philosophy, applying the philosophy of science to psychiatry. But there was no interest in psychiatry in anything that challenged their core beliefs, so I thought I would move. However, I knew it would not be any different in any other city, so I decided on a complete change rather than half a change.

I went there because I could already tolerate isolation (overwhelmingly, psychiatrists cannot). And I very quickly learned that most of what I had been taught simply was not correct, even at the most practical levels. For example, in that fiendishly hot climate with punishing levels of humidity, it is not possible to use lithium or drugs that suppress sweating. So I learned to do without them. Electroconvulsive therapy was not available, so I managed without it. More important, what was regarded as schizophrenia in Aboriginal people actually wasn’t. If they were simply watched for a while, most of them got better with very little medication. However, if they were put on depot antipsychotics, they quickly got worse, which led to more drugs, which made them worse again, and they did not recover.

AFTAB: You have commented on how the current practice of psychiatry tends to ignore personality disorders, and the notion of personality dysfunction as a cause of psychiatric syndromes (former axis I) such as major depression is largely discounted. This is consistent with my clinical experience as well. For instance, psychiatry recognizes that individuals with personality disorders are more likely to have treatment resistant depression, yet the treatment algorithms for treatment resistant depression do not really take that into account. And, in practice, that leads to aggressive pharmacotherapy. Does this help explain why treatment resistance appears to be the rule rather than the exception in clinical settings?
ality is everything. Ignore it at your patient’s peril.

AFTAB: If I were to try to capture the essence of the biocognitive model in a sentence, I would say: Mental disorders are psychological disorders created by information processing feedback loops gone awry in biologically intact brains. Is this a fair characterization? How would you succinctly describe the biocognitive model?

MCLAREN: That is indeed a fair characterization. The essence of the model is that self-reinforcing processing disorders can arise in perfectly healthy brains and, in the overwhelming majority of cases, that is exactly what happens. A small problem starts, then gets worse, then it causes further complications, then the person tries to rectify it—often by self-destructive means such as drinking or social isolation, which results in more complications, and so it goes. This isn’t rocket science, it is essentially chaos theory with a human face.

AFTAB: If your biocognitive framework for understanding mental disorders is correct, then why should psychiatry be seen as a medical specialty? If there is no underlying biological dysfunction, then why are physicians better qualified (than say, psychologists) to take primary ownership of the diagnosis and treatment of psychological disorders?

MCLAREN: This is a very important question. We could abolish psychiatry today but by early next week we would have to reinvent it because humans are minds and bodies, not mindless bodies. I tell medical students and residents that they have to take a medical history and be prepared to examine the patient because if they do not, the next person to do so may well be the pathologist. Anxiety, for example, affects every part of the body, from the scalp (piloerection) to the soles of the feet (sweating), and we have to sort through what’s what. Only an experienced medical practitioner can do that, and the more experience you have, the better.

Only yesterday morning, I had to deal with a young woman with abdominal symptoms, dismissed as psychosomatic by the hospital. In fact, she had severe colonic dysfunction and impaction due to the massive doses of drugs she was prescribed. The last patient for the day was a young man with frontal brain damage, severe anxiety, and intractable headaches who limped because of severe cellulitis of both legs. The last thing he wanted was to go to hospital because they invariably would dismiss him as mad. We are doctors, and when everybody else does not want to know the patient, we still care. Clinical neuroscientists? What grandiose, narcissistic rubbish.

AFTAB: Would you consider your biocognitive model of mental disorder to be scientific in nature or philosophical? If you consider it to be scientific, what makes it scientific? The model relies heavily on philosophical ideas of David Chalmers, PhD, and Alan Turing, PhD, and I am not entirely sure if it makes any falsifiable predictions. (And if the biocognitive model is indeed primarily philosophical, then how does it help psychiatry become a more scientific specialty?)

MCLAREN: How much space do I have? It is a dualist model, so in that sense, it is primarily a philosophical model, staking out a particular ontological stance. However, it is not substance dualism, because that only goes into an infinite regress, so it is nonscientific. It is scientific in the sense that it starts with a set of axioms that sit firmly within the framework of current scientific thinking. I am working on a mathematical derivation of an emergent informational model of mind, the mind as an informational space. This is not easy—I am not a mathematician—so I struggle through texts such as George Boole’s Laws of Thought. He showed how we could use a dual-valued or binary algebra (now known as Boolean algebra) to duplicate the processes of reasoning, out of which came the entire informational revolution of the 20th century. OK, so reasoning is the easy part, the low-hanging fruit of a data-processing model of mind. Now we move onto what Chalmers has called the hard problem of consciousness sensory experience. Chalmers argues that the mind arises from, or supervenes upon, the brain by rational processes governed by laws of supervenience that we can determine. I am working on the case that his laws of supervenience are, in fact, no more than Boole’s Laws of Thought. This is really interesting; this is the future of psychiatry, especially when we have just been told what I had warned 27 years ago—that biological psychiatry has limits1 and it cannot tell us all we need to know about mental disorder. This is what residents and young psychiatrists should be looking at, not wondering whether a bigger genome-wide association study will give the answers. It won’t.2 As for refutable predictions, here’s one: Nobody will ever find anything in the brain that could conceivably account for a single mental disorder.

AFTAB: You have also been a critic of the psychiatric publishing industry. One of your arguments is that psychiatric journals do not have a declared model of mental disorder. In Humanizing Psychiatry, you wrote: “Of the major, English language journals of general psychiatry still in print, not one nominates a model of mental disorder in its instructions to authors.”3 and “Currently, no psychiatric journal in the world meets minimum criteria for a journal of scientific record. Of 28 prestigious journals reviewed, not one defined the model of mental disorder that guides its publications policy.”4 I do not know if journals in other fields of medicine would stand up to this sort of scrutiny. For instance, I do not think neurology journals (like Neurology) or general medicine journals (like the Journal of the American Medical Association or New England Journal of Medicine) endorse any particular model in their instructions to authors.

MCLAREN: The simple answer is that mainstream medical journals do not make any claims above and beyond the established limits of reductionism, so they all meet the criterion. For them, it works because they very carefully stick to the fields for which it was designed. Reductionism works fine if you are peering...
down a microscope at a nephron or squirting antibiotics into an IV line. It is only when we move beyond the narrow confines of physical medicine and try to throw a reductionist net over irreducible phenomena such as language, emotions, and so on that we run into trouble. Psychiatrists did not know that 40 years ago when they launched DSM-III, but they should have. Worse still, they painted themselves into a reductionist corner without leaving themselves an escape route, and reductionism has failed.

AFTAB: Does the biocognitive model offer any guidance regarding how to draw the boundary between disorder and normal? What makes a condition a “disorder”?

MCLAREN: There is always going to be a social element in the definition of disorder; we cannot escape it. However, we need to pull right back from the notion of imperial psychiatry unlimited, which remorselessly intrudes on normality. I think what Allen Frances, MD, said in his contribution to this series—a concept that is, in my opinion, absolutely correct: Life isn’t always a barrel of fun, but that’s not mental disorder. People recover from adversity; they are very resilient creatures. But when they cannot recover, when they become trapped in a self-reinforcing cycle of mental distress and social failure, then it becomes a disorder. This says that we cannot impose treatment on people just because they do strange things like hear voices—as long as they are not damaging themselves or anybody else.

AFTAB: Academic work in philosophy of psychiatry has generated a lot of articles in recent years, why do you think they are not making the sort of contribution you feel psychiatry needs?

MCLAREN: This is true, there are such papers, but they are few and far between. Also, they are mostly published by senior figures in psychiatry who are deeply committed to the current paradigm, not young radicals who want to analyze the paradigm itself. These types of papers are tentative suggestions on how we can improve psychiatry without rocking the boat too much. I have never worked in academia; I spend all day, every day assessing and treating unselected public patients and then write my reports and research papers at night. I have no affiliations, but I have a breadth and depth of experience in psychiatry that academic psychiatrists can never have. I also have formal training in philosophy, and I think reductionist biological psychiatry cannot be saved by a few cosmetic changes. It is doomed to fail, just because it does not have, and never can have, a heuristic model of mental disorder. I accept that, so I stand outside mainstream psychiatry with a sledgehammer saying, “Let’s get on with wrecking this mess and start again.” Time will tell who is right, but when we look at how much money and effort has been spent on trying to build a science of biological psychiatry, you wonder why anybody bothered.

AFTAB: Any words of advice for younger psychiatrists?

MCLAREN: Yes, I have, and thank you for asking. My advice is this: Get out of the echo chamber of modern psychiatry. Get out of the huge, luxurious inner-city hospitals where academics live in a permanent intellectual bubble. Challenge everything you are told, and insist the professors answer your criticisms. Go out into the real world; work in prisons, in run-down towns with high unemployment or with refugees or in remote areas. Go overseas or into underprivileged parts of your own country. And that is how you learn about real psychiatry. Oscar Wilde said, “An idea that is not dangerous is unworthy of being called an idea at all.” I firmly believe that.

AFTAB: Thank you!

CONVERSATIONS IN CRITICAL PSYCHIATRY

Philosophy and Psychiatry (AAP) and has been actively involved in initiatives to educate psychiatrists and trainees on the interaction of philosophy and psychiatry. He is also on the Psychiatric Times Advice Board. He can be reached at awaisaftab@gmail.com.

Dr Aftab would like to thank Yash Joshi, MD, PhD, for his valuable input regarding the works of Dr McLaren and this interview.

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

Disclosures
Dr Aftab and Dr McLaren report no financial disclosures and conflicts of interest.

REFERENCES

Dear Provider

Richard M. Berlin, MD

My parents named me Richard just because they liked the name, clueless about how fast King Richard the Lionhearted could become Little Dick when a Jersey bully taunted me.

And I felt taunted today when I read Dear Provider in a letter from a health care company. Provider is a fine word, and I’ve always felt proud to provide for my family, but the company doesn’t know guys from Jersey are sensitive, that I felt devalued, my hard earned Doctor mixed into an alphabet soup of colleagues from scores of disciplines who share patient care. The company’s game: blend us together, pay everyone less, and increase profits which is precisely what I provide for them.

Right now, I’ll ignore the bully’s insult, let them know Dear Doctor will be fine next time. But call me Dear Provider again and it’s a Jersey street fight with a doctor who can be a real dick.

Dr Berlin is Instructor in Psychiatry, University of Massachusetts Medical School, Worcester, MA.
Why You May Want to Swipe Left on Social Media

Jessica Lipschitz, MD, and John Torous, MD

W e have all been there. In an idle moment, you instinctively reach for your smartphone to browse your social media feed. The goal is simple: an easy distraction. But the effect is sometimes complicated. Many of us enjoy social media to stay connected with friends, family, colleagues, or groups of individuals with similar interests, but there is inherently an ugly side too. That side where you see something—the perfect family photo, the vacation picture, the promotion of a work accomplishment—and think, “I wish that were me,” can have negative mental health effects.

These double-sided reactions to social media are critical to understand given the high rates of exposure so many people around the globe have to social media each day. In 2018, average daily social media use among internet users worldwide was 2 hours and 16 minutes.1 And, while user retention for most apps over the first 90 days is estimated between 10% and 30%, many social media apps have retention rates ranging from 60% to 98%.2,3 But are they good for us or are they just addictive? Perhaps they are the social-emotional equivalent of eating fast food every day for lunch.

Several lines of research may be relevant in answering this question. For example, social comparison theory would have us speculate that when we are offered highly curated pictures of other people’s lives, we tend to feel worse about our own.4 Similarly, mindfulness, or focusing on the present moment on purpose without judgement, has been found time and time again to be linked to emotional wellbeing. To the extent that social medial calls for a focus on documenting our most precious moments rather than living them, we might expect that users focused on posting pictures or videos of these moments may be a little less present in those moments.

The difficulty in answering this question is that most of the studies evaluating the social and emotional impact of social media have been cross-sectional. They only look at one point rather than how engaging with social media affects users over time. From cross-sectional studies, we know some things. For example, more than 1 hour of screen time daily has been associated with worse psychological well-being (Figure).5 Findings from another large national study of young adult social media users indicates that those who used a large number of platforms (7 to 11 different social media platforms) were 3 times more likely to have symptoms consistent with a mood or anxiety disorder.6

The challenge of these studies is that they do not tell us whether use of social media makes people unhappy. Cross-sectional studies focus on describing patterns observed (for example, that individuals with high amounts of screen time or who use more platforms are more often unhappy), but not why those patterns are observed. From these findings two different scenarios are entirely possible. First, it may be that people who are more depressed use social media more often in an attempt to feel better. Second, it may be that people who use social media more often become more depressed because they are less mindful in their day-to-day lives or are more engaged in destructive social comparison practices. Either explanation, and perhaps they are the social-emotional equivalent of eating fast food every day for lunch.

Several studies have been conducted to help answer this question. For example, in one study, participants were assigned an intervention. The app intended to reduce use of social networking addiction.8

Dr. Lipschitz is Associate Director, Brigham and Women’s Hospital Digital Behavioral Health and Informatics Research Program, Boston, MA. Dr. Torous is Director of Digital Psychiatry, Beth Israel Deaconess Medical Center, Boston, and Chair, American Psychiatric Association, Health Information Technology Committee.

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3. Chen A. New data show losing 10% of mobile users is normal, and why the best apps do better. 2018.

Figure. Relative risk in the last 12 months among 14- to 17-year-old high users of screens (7+ hours/day versus low users of 1 hour/day)
Understanding Long-Acting Injectable Antipsychotics for Better Treatment Adherence

Michael W. Jann, PharmD

**CASE VIGNETTE**

"John" is a 24-year-old male who 6 months ago received a diagnosis of schizophrenia. After successful initial treatment with an oral antipsychotic, he felt no further need to take his medications. Subsequently, over the next several months, his family noticed that delusional symptoms began reappearing and withdrawal behaviors from current activities increased. At his next outpatient appointment, the prospect of a long-acting injectable antipsychotic was introduced. Initially, John refused the injectable antipsychotic saying that he can take oral medications. Over the next 2 weeks, his family noticed that only part of his medication was taken and, when looking over the number of tablets, it appeared that John was taking about half of his medication. His clinician told him that if inconsistent adherence to treatment continues, the symptoms likely will not get better and could get worse. If the symptoms and his thinking get worse, he may need to be hospitalized.

The option of a LAI was reintroduced. Although John was seemingly reluctant, he was convinced by the treatment team and agreed to give the LAI a try for the next few months. His family whole-heartedly supported the LAI option knowing that this option would eliminate gaps in his pharmacotherapy.

ACTIVITY GOAL
The goal of this activity is to provide an understanding of long-acting injectable antipsychotics and how they can benefit treatment adherence.

LEARNING OBJECTIVES
After engaging with the content of this CME activity, you should be better prepared to:

- Identify the formulation differences between oral and long-acting injectable (LAI) antipsychotics.
- Assess the efficacy and safety profiles of LAI second-generation antipsychotics.
- Discuss LAI antipsychotics as they relate to treatment adherence.

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

ACCREDITATION/CREDIT DESIGNATION/FINANCIAL SUPPORT
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EXPIRATION DATE: September 20, 2021
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Long-acting injectable (LAI) antipsychotics address both adherence and nonadherence issues. Fluphenazine enanthate, a first-generation antipsychotic, became available as a LAI in the US in the 1960s; fluphenazine decanoate LAI became available in the 1970s; and haloperidol decanoate LAI became available in the 1980s. The first second-generation antipsychotic LAI, risperidone microsphere, was FDA approved in 2003. Only three other LAI second-generation antipsychotics are currently available: olanzapine pamoate, paliperidone palmitate, and aripiprazole palmitate (available as monohydrate and lauroxil formulations). Paliperidone palmitate has two formulations for monthly or three-month injection intervals. Aripiprazole lauroxil also has formulations that allow for monthly, a 6-week, or 8-week administration intervals.

Formulation, pharmacokinetics, and dosing

The process to develop LAI antipsychotic formulations represents significant technological challenges and opportunities. Based on their chemical structure, not all antipsychotics are available as a LAI formulation. LAI formulations impose their pharmacokinetic profiles, initial dosing requirements, storage conditions, and utilization methods as well as the ability to slowly release the body over an extended time period. LAI fluphenazine and haloperidol are basically esters that are dissolved in sesame oil. LAI second-generation antipsychotics are aqueous preparations with different formulations. Only risperidone microspheres are given at 2-week intervals; the other LAI second-generation antipsychotics are administered from monthly to as long as every 3 months (olanzapine pamoate microcrystals, paliperidone palmitate Nanocrystals, and two aripiprazole preparations: a lyophilized monohydrate and a prodrug approach with the N-acloxyethyl molecule). These formulations account for their different pharmacokinetic profiles and dosing practices. The common thread is that the dosing interval is extended beyond daily oral dosing.

The key concept for LAI antipsychotics is that the time to reach steady-state conditions takes longer than an oral formulation as the drug is gradually released from the deltoid (also the glutus maximus) muscle injection site. Because of this, oral antipsychotics are typically needed for about 2 to 3 weeks when LAIs are started. However, there are exceptions:

1. Paliperidone palmitate dosing starts at 234 mg followed by a 156 mg second administration one week later and reaching therapeutic plasma concentrations within a few days.

2. Olanzapine pamoate reaches peak plasma concentration 2 to 4 days after injection with an elimination half-life of 2 to 4 weeks.

3. Aripiprazole lauroxil has a 1-day treatment initiation option where the patient can receive a single 662-mg aripiprazole lauroxil injection plus 30-mg oral aripiprazole followed by either 441-mg or 882-mg aripiprazole lauroxil injection.

After initiation, LAI antipsychotics can be administered monthly or every 4 weeks. Paliperidone palmitate can be given every 3 months, but only after the patient has been stabilized with the monthly formulation for at least 4 months—with the last two injections at the same dose. Monthly LAI aripiprazole lauroxil has two additional formulations with administration every 6 or 8 weeks.

To provide further dosing flexibility for patients and providers, LAI antipsychotics can be administered +/- 1 week for the monthly dosing intervals allowing for possible changes in the patient’s appointment schedule. This also applies to the 3-month paliperidone palmitate preparation with a +/- 2-weeks for the every 3-months dosage schedule. (For more information on dosing, missed doses, and switching strategies see Samani et al. and Magnisson et al.)

Summary of clinical studies

There is a large body of clinical studies on LAI second-generation antipsychotics including those leading to regulatory agency approval as well as real-world studies. The latter study types provide clinicians with a comprehensive look at various clinical situations.

LAI second-generation antipsychotics are FDA approved for the acute and/or maintenance treatment of schizophrenia. The LAI formulations have several additional indications: monthly paliperidone palmitate is FDA approved for schizoaffective disorder; risperidone and aripiprazole monohydrate are FDA approved for bipolar disorder.

Clinical studies designed for regulatory agency review typically follow a specific design methodology. For example, patients are randomly assigned to a placebo control group and compared to one or more doses of the antipsychotic. LAI antipsychotic doses are usually fixed doses to accurately determine the drug’s efficacy and safety profiles. The study duration for acute exacerbation of schizophrenia is about 12 weeks. The primary efficacy outcome measure uses the Positive and Negative Syndrome Scale (PANSS) where the total score decreases from baseline to the study endpoint and demonstrates a statistical significance from the placebo group.

The study design for a maintenance study with a LAI antipsychotic is more complex with two main phases in a trial: an open-label phase and a double-blind phase. At a minimum, the open-label phase consists of different stages where patients are switched to the LAI formulation of the antipsychotic being studies, and then to a tolerability phase. The next step is being stabilized on either the oral formulation or directly to a LAI antipsychotic (plus an oral dosing overlap if needed). The subsequent stage proceeds with LAI administration with the study agent with continued stabilization. These stages can last from 9 weeks up to 36 weeks depending on study design. Finally, LAI second-generation antipsychotics are evaluated in a 52-week, double-blind, and placebo control phase.

The primary outcome measure is the time for patient relapse. In the monthly paliperidone palmitate study, relapse was defined as hospitalization, an increase in total PANSS or an increase on any specified PANSS item (eg, delusions) for two consecutive assessments, and deliberate self-injury or aggressive behavior and suicidal or homicidal ideation deemed significant by the clinician. For the 400 mg aripiprazole monthly dose study, the primary outcome was time to relapse of psychotic symptoms and/or impending relapse defined as any or all 4 criteria on the Clinical Global Impression Scale (CGIS), risk of suicide as defined by the CGIS, an increase on any individual PANSS item (eg, hallucinatory behavior), hospitalization, or violent behavior.

The study design was similar for the 3-month paliperidone palmitate preparation; however, the trial consisted of the monthly formulation (transitional phase) followed by one injection of the 3-month formulation (maintenance phase), and finally the double-blind, placebo-controlled phase. The primary outcome was relapse where relapse rates and time to first relapse were calculated. Relapse was defined as hospitalization, an increase level of care, an increase of 25% in the total PANSS score, or an increase of 10 points if the baseline total PANSS was less than 40. Clinical situations such as deliberate self-injury, suicidal or homicidal ideations, violent behavior or property damage, or a change in the CGIS score to 6 or 7 were also included in the relapse criteria.

These complex study designs are necessary to establish objective and subjective patient stability prior to the testing conducted in the double-blind, placebo-control phase. Therefore, when a relapse episode takes place, its occurrence is defined and scored by a binary process (eg, yes/no).

Each of the studies with monthly LAI second-generation antipsychotics showed efficacy. Patients had significantly fewer (P < .05) relapse and hospitalization rates. LAI antipsychotics with a longer than monthly administration interval have unique qualities when undergoing efficacy analysis. The 3-month pal-
Table. Summary of the pros and cons of oral antipsychotics versus LAI antipsychotics

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<th>Criteria</th>
<th>LAI antipsychotic</th>
<th>Oral antipsychotic</th>
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<td>Cost</td>
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<td>Adherence</td>
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*aEqual efficacy among all antipsychotics except clozapine.
*bEqual safety profiles except the LAI olanzapine pamoate, which has a warning regarding post-injection delirium sedation syndrome.

LAI, long-acting injectable; X, favors.

risperidone palmitate clinical trial interim analysis for delaying time to relapse was significant in favor of the active agent compared with placebo (P < .001) with the median time to relapse of 274 days. The relapse rate for 3-month paliperidone palmitate compared with placebo group was substantially lower (9% versus 29%, respectively).

LAI first-generation versus second-generation
LAI risperidone was not available to providers until 2003. Yet, the question of comparing a first-generation antipsychotics with a second-generation antipsychotic presented clinicians with an intriguing issue. For example, how to design a study that can equally compare a first-generation to a second-generation antipsychotics. A double-blind clinical study (funded by Janssen, the manufacturer of risperidone) evaluated oral risperidone (mean ± SD dose 4.9 ± 1.9 mg) versus oral haloperidol (mean dose 11.7 ± 5.0 mg).4 The study was undertaken to examine relapse prevention in outpatients with schizophrenia or schizoaffective disorder (N = 397) with an extensive criteria defined for relapse. The results indicated a higher relapse rate for haloperidol (risk ratio = 1.93, 95% CI = 1.33 – 2.80, P < .001) versus risperidone.

Another study compared LAI risperidone with a psychiatrist’s choice of oral antipsychotics in unstable schizophrenia or schizoaffective disorder.4 A total of 382 patients were enrolled in the study and randomized to receive LAI risperidone or continue on their oral antipsychotic. The findings indicate that LAI risperidone was not superior to the oral antipsychotics in preventing hospitalizations rates (39% after 10.8 months versus 45% after 11.3 months (respectively), hazard ratio (HR) = 0.87, 95% CI = 0.63 – 1.20). Moreover, there were no significant differences in survival and health service use.

The ACLAIMS clinical trial compared 1-month paliperidone palmitate with haloperidol decanoate in patients with schizophrenia or schizoaffective disorder.5 The primary criteria for efficacy failure included psychiatric hospitalization, need for crisis stabilization, increased frequency of outpatient visits, ongoing or repeated need for adjunctive oral antipsychotic medications, and several other reasons regarding transitioning from previous oral to injectable antipsychotics. No statistically significant differences between 1-month paliperidone palmitate and haloperidol decanoate in efficacy failure (HR = 0.98, 95% CI = 0.65 – 1.47) were found, which indicates that the antipsychotics were equally effective in preventing relapse.

Taken together, the results of these comparative studies of first-generation versus second-generation antipsychotics are reasonable given their pharmacologic profiles for dopamine receptor subtype 2 antagonism. The addition of serotonin 5-HT2A antagonism for risperidone and paliperidone is representative of most second-generation antipsychotics.

Examining and comparing safety profiles
The overall outcomes from the LAI second-generation antipsychotics studies found no new concerns regarding safety information. The only exception where a LAI second-generation antipsychotic differs in the safety profile from its oral counterpart is olanzapine pamoate. Approved by the FDA in 2009, olanzapine pamoate has a warning regarding post-injection delirium sedation syndrome, which occurs when the drug is inadvertently administered into a blood vessel, which leads to rapid drug release. The resulting symptoms are delirium, ataxia, confusion, or altered consciousness, thus the FDA requires that patients remain at their treatment facility for 3 hours post-injection.

For second-generation LAI antipsychotic usage, after establishing tolerability with the corresponding oral antipsychotic, the long-term safety monitoring should be ascertained using recommended guidelines where available. Providers should exercise their clinical assessments balancing benefits versus risk especially when LAI second-generation antipsychotics are prescribed. (For detailed information on adverse effects, the reader is referred elsewhere.)

When treating with LAI second-generation antipsychotic, long-term monitoring is needed for metabolic syndrome, extrapyramidal effects (especially tardive dyskinesia), and hyperprolactinemia. For metabolic syndrome guidelines include monitoring of weight, fasting blood glucose, HbA1c, and lipid profiles at various treatment intervals.6

Findings suggest a relatively low occurrence of akathisia with LAI second-generation compared with LAI first generation antipsychotics. The incidence of akathisia was significantly greater for haloperidol decanoate compared with once-monthly paliperidone palmitate (10.6% versus 2.8% respectively, P = .006).7 The incidence was comparable to that of LAI aripiprazole lauroxil.8

A baseline Abnormal Involuntary Movement Scale (AIMS) exam is recommended before any antipsychotic medication is initiated; it should be repeated at least every 6 months with first-generation antipsychotics and annually with second-generation antipsychotics. Another safety difference reported in the clinical trial between haloperidol decanoate and 1-month paliperidone palmitate was the elevation of prolactin concentrations, but the incidence of sexual adverse effects, galactorrhea, and gynecomastia was not different.9 There were significant differences in serum prolactin concentrations (mean, 95% CI) between haloperidol decanoate and 1-month paliperidone palmitate in men (15.41 µg/L, 10.73 - 20.08 versus 34.56 µg/L, 29.75 - 39.37; respectively, P < .001) and women (26.84 µg/L, 13.29 - 40.48 versus 75.19 µg/L, 63.03 - 87.36; respectively, P < .001). However, no clinical significant differences were found on sexual dysfunction scores (I7 19) using the Arizona Sexual Experiences scale in men (39.4% versus 37.8%; respectively, P = .77) and women (73.1% versus 72.7%; respectively, P = .88).

Elevated prolactin levels are known to occur with risperidone and paliperidone, but the long-term consequences remain to be elucidated. Prolactin levels remain relatively neutral with aripiprazole.

Communication strategies and considerations
Theoretically, any patient needing long-term maintenance antipsychotic treatment is a candidate for LAI antipsychotics. A pro and con summary of antipsychotics versus oral antipsychotics is presented in the Table, which can help when discussing treatment decisions with patients. LAI second-generation antipsychotics are typically more expensive than oral antipsychotics.

The Case Vignette describes the initial challenges for treatment providers and the need to...
collaborate with the patient in offering a LAI antipsychotic. LAI second-generation antipsychotics are preferred over first-generation antipsychotics because of fewer extrapyramidal adverse effects. There are advantages for LAI antipsychotics because the clinician has reliable information on how much medication was given during treatment. Moreover, patient adherence with oral antipsychotics can be overestimated and nonadherence underestimated by providers and caregivers.

Patients should be asked about adherence at every visit in a respectful manner without placing blame on any missed doses. Patients often decline appointments—clinicians have time to work with the patient on adherence. Although, there are no guarantees with LAI antipsychotics to offer a viable option to help with medication adherence and reduce any potential gaps in treatment.

**REFERENCES**


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  - Manhattan, NY

- **Consultation Liaison Psychiatrist**
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  - New York State University Hospital, NY

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- Visa sponsorship opportunities

Take the first step in joining one of our teams and contact LaTreese Phillips at (916) 691-4818 or CentralizedHiringUnit@cdcr.ca.gov.

You may also apply online at www.cchcs.ca.gov.

PSYCHIATRISTS

$266,844 - $320,640 annual salary (Board Certified)

$260,004 - $311,592 annual salary (Board Eligible)

INPATIENT • OUTPATIENT

Division of Behavioral Health Services

wellness recovery prevention

laying the foundation for healthy communities, together

The State of New Jersey’s Division of Behavioral Health Services is seeking motivated Psychiatrists for full-time inpatient work in our Joint Commission accredited State psychiatric hospitals and forensic center. Psychiatrists with management experience are also needed to serve as Chiefs of Psychiatry.

Post Certified - $205,541 (2 years post certification)
Board Certified - $237,817
Board Eligible - $224,080

- Facilities are in close proximity to metropolitan centers of New York City and Philadelphia/N.J. Shore
- Psychiatrists work with a multidisciplinary team
- Primary care physicians provide for patient’s physical health care
- University affiliations/opportunities to work with forensic fellows and psychiatry residents
- On-site CME activities and paid CME leave time
- 35 hour work week
- Generous compensation for voluntary on-call available
- Private Practice Permitted
- 12 paid holidays
- Generous medical and dental benefits and retirement packages for full-time positions

Candidates must possess N.J. medical license

The Department of Health welcomes J1 Visa/Conrad 30 Program applicants. Additionally, the Department participates in a variety of State and federal workforce development and incentive programs ranging from, but not limited to the Federal Student Loan Redemption department’s tuition reimbursement program as well as being a designated site for NIDA-funded research on addiction. SSTAR is a Certified Community Behavioral Health Clinic with SAMHSA-funded opportunities for service innovation, including technology supports for wellness and recovery, and acupuncture. Fall River is one hour south of Boston, MA a half hour from Providence, RI and 45 minutes from Cape Cod, MA. We are a designated site for state/federal health professional loan repayment programs.

For more information visit www.sstar.org or email lmachado@sstar.org

SSTAR in Fall River, MA is seeking psychiatrist(s) to join our treatment and leadership team.

SSTAR is a non-profit healthcare agency with an international reputation as a leader in the provision of integrated primary care, mental health, and substance disorder treatment as well as being a designated site for NIDA-funded research on addiction. SSTAR is a Certified Community Behavioral Health Clinic with SAMHSA-funded opportunities for service innovation, including technology supports for wellness and recovery, and acupuncture. Fall River is one hour south of Boston, MA a half hour from Providence, RI and 45 minutes from Cape Cod, MA. We are a designated site for state/federal health professional loan repayment programs.

For more information visit www.sstar.org or email lmachado@sstar.org

STARR Psychiatric – Medical Director

Full or Part-Time

STARR in Fall River, MA is seeking psychiatrist(s) to join our treatment and leadership team.

STARR is a non-profit healthcare agency with an international reputation as a leader in the provision of integrated primary care, mental health, and substance disorder treatment as well as being a designated site for NIDA-funded research on addiction. SSTAR is a Certified Community Behavioral Health Clinic with SAMHSA-funded opportunities for service innovation, including technology supports for wellness and recovery, and acupuncture. Fall River is one hour south of Boston, MA a half hour from Providence, RI and 45 minutes from Cape Cod, MA. We are a designated site for state/federal health professional loan repayment programs.

For more information visit www.sstar.org or email lmachado@sstar.org

PSYCHIATRISTS

$266,844 - $320,640 annual salary (Board Certified)

$260,004 - $311,592 annual salary (Board Eligible)

INPATIENT • OUTPATIENT

California Correctional Health Care Services is seeking proactive, knowledgeable psychiatrists to join our multidisciplinary teams. Within the California Department of Corrections and Rehabilitation’s facilities, you will find like-minded professionals well-versed in the intricate psychiatric and medical interplay necessary to treat our diverse patient population. Here, you will see and develop treatment plans for cases you won’t encounter in any other practice. And with the support of our dedicated medical assistants, you’ll be able to devote your time to practicing and honing advanced psychopharmacological skills. Plus, with locations throughout California, you’re sure to find your perfect fit.

In return for your efforts, we offer:

- 40-hour workweek with flexible schedules, including 4/10s
- Generous paid time off and holiday schedule
- 401(k) and 457 plans (tax defer up to $39,000 - $52,000 per year)
- State of California retirement that vests in five years
- $10,000 Thank You Bonus to professionals newly hired with the State of California
- Relocation assistance available to professionals newly hired with the State of California
- Paid insurance, license, and DEA renewal
- Visa sponsorship opportunities

Take the first step in joining one of our teams and contact LaTreese Phillips at (916) 691-4818 or CentralizedHiringUnit@cdcr.ca.gov.

You may also apply online at www.cchcs.ca.gov.

Visit us at APA Annual Meeting

Booth #646
UMass Memorial Medical School

Senior Vice President and Chief of Staff, The Menninger Clinic
Vice Chair, Menninger Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine

As Chief of Staff at The Menninger Clinic, you will be a key member of the executive leadership team and play a vital role in propelling Menninger toward its 100th anniversary in 2025 and beyond. As Vice Chair of the Department, you will be a member of the Executive Committee, led by the Chairman of the Department and a leader in the overall clinical, research, and educational missions of the Department. This is an exciting opportunity for a dynamic, experienced physician executive to join the leadership team at a growing, high-calibre mental health system.

The Menninger Clinic (www.menningerclinic.org), under the new leadership of Armando E. Colombo, is one of the nation’s premier mental health care providers with an outstanding environment of care and expanding continuum of services. Menninger is the private psychiatric teaching hospital for BCM (www.bcm.edu), a leading academic health science institution known for excellence in education, research, health care and community service.

Position Summary and Responsibilities:
The Chief of Staff is the principal medical and clinical authority at Menninger, over all the departments, services and sections of the Medical Staff. The Chief of Staff leads the direction and oversight of medical and psychological care, as well as teaching, continuing education and research activities. The Vice Chair collaborates with others and engages in scholarly work as reflected in publications and invited presentations.

Position Qualifications:
Applicants qualified for Associate Professor or Professor academic ranks will be considered. Must have an MD or DO degree with completion of an approved residency in general psychiatry and board certification in psychiatry. Must hold or be able to obtain a current license to practice medicine in the state of Texas. Minimum of seven years in clinical practice, administration of complex clinical programs/medical organizations and demonstrated competency in supervision of medical and clinical professionals. Requires prior experience as a senior medical executive in an academic department of psychiatry. Applicants must have depth of management experience and knowledge in areas of leadership, communication, rationality and accountability, delegated authority, performance, effectiveness, participatory management, and financial management. Preferred: Maintains a national reputation of psychiatric excellence and is acknowledged as an industry leader.

Baylor College of Medicine is an Equal Opportunity/Affirmative Action/Equal Access Employer.

Interested Applicants:
Please apply online at www.bcm.edu in the faculty careers section (direct link to posting https://bit.ly/37wnqVr), and provide a brief cover letter and CV to:

Wayne K. Goodman, MD
Professor & Chair, Menninger Department of Psychiatry & Behavioral Sciences
Baylor College of Medicine
One Baylor Plaza; MS: BCM350
Houston, TX 77030
wayne.goodman@bcm.edu

Facility Medical Director (Cape Cod and Islands Mental Health Center, Pocasset, MA): Provides administrative and clinical oversight for the DMH-operated and contracted state hospital and community support programs. Clinical Care in our Partial Hospital program.

Full-Time Inpatient Psychiatrist (Cape Cod and Islands Mental Health Center, Pocasset, MA): Work closely with two psychiatric APRNs, a consulting internist, and a multidisciplinary team.

Full-Time Inpatient Psychiatrist (Taunton State Hospital, Taunton, MA):
Inpatient services while providing acute clinical care

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

Full-Time Psychiatrist (Corrigan Mental Health Center, Fall River, MA):
Outpatient and partial hospital services, as well as coverage of a 16-bed inpatient unit.

Inpatient Psychiatrist (Worcester Recovery Center and Hospital, Worcester, MA):
Be part of a person centered, recovery oriented multidisciplinary team that strives to help individuals lead healthy lives and return safely to the community.

For additional information, please contact:
Marie Hobart, MD, Vice Chair, Public Sector Psychiatry
marie.hobart@umassmed.edu
Geoffrey Bottone - geoffrey.bottone@umassmed.edu.

Interested applicants should apply directly at www.academicjobsonline.org (J-1 and H-1B candidates are welcome to apply)

UMass Memorial Health Care

Chief Medical Officer (CHL, Worcester, MA):
Supervision of a large group of professionals and participation in development efforts serving >22,000 individuals each year.

Medical Director (Adult Outpatient Psychiatry, Worcester, MA):
Clinical Academic oversight of a new 38-office outpatient teaching clinic

Medical Director (Adult Inpatient Psychiatry, PTRC, Worcester, MA):
Provide psychiatric and medical supervision and direction to mental health and substance abuse services to a 26-bed locked unit.

Adult Outpatient Attending Psychiatrist (CHL, Worcester, MA): Outpatient clinic in Worcester serving a diverse population with mental health and substance use disorders.

Adult Inpatient Attending Psychiatrist (PTRC, Worcester, MA):
Inpatient services while providing acute clinical care

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

Interested applicants who submit a letter of interest and curriculum vitae addressed to Sheldon Benjamin, MD:
c/o: Jessica Saintelus, Physician Recruiter
Jessica.Saintelus@umassmemorial.org
http://jobs.jobvite.com/umassmemorialmedicalgroupphysicians/search?r=d&P=Psychiatry

As the leading employer in the Worcester area, we seek talent and ideas from individuals of varied backgrounds and viewpoints.
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Choose your own hours  
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Earn over $350K/Year

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Los Angeles/Orange County Area  
Sacramento Area  

Comprehensive Psychiatric Services  
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F 925-944-9709  
druzuberi@psych-doctor.com  

www.psych-doctor.com

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**New York**

**PSYCHIATRIST**

Earn over $350K/Year

Benefits includes:  
Malpractice ins, 401K, Medical Dental, Vision & LTD ins

Santa Clara Valley Health and Hospital System, a public healthcare system in the heart of Silicon Valley, is seeking BE/BC psychiatrists & PGY-III/IVs for a variety of clinical settings, including emergency psychiatric services, inpatient psychiatric services, outpatient behavioral health clinics, and custody health programs.

Opportunities for additional moonlighting also exist within our healthcare system.

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

Psychiatrists are eligible for numerous benefits including 7 weeks of annual leave, 1 week of educational leave, 12 holidays, $4500 educational funds, health benefits, life insurance and CalPERS retirement plan.

If you are interested in working in a dynamic and collegial work environment, please submit a CV and letter of interest directly to:

Dr. Tiffany Ho  
Behavioral Health Medical Director  
tiffany.ho@hhs.sccgov.org  
(408) 885-5767  
The County of Santa Clara is an Equal Opportunity Employer

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**Telecare Corporation**

BE or BC psychiatrist needed.  

Following locations have immediate openings:

- **San Jose, CA:** Schedule: 40hrs per week. Pay Rate: $291,200 - $364,000 per year! Excellent Benefits.
- **San Jose, CA:** Schedule: 8-20 hours per week; Pay Rate: $140 - $175/hour (Employee); $183 - $225/hour (Contractor)
- **Belmont, CA:** Schedule: 24 hours per week; Pay Rate: $140 - $158/hour (Employee); $183 - $205/hour (Contractor)
- **Sacramento, CA:** Schedule: 16 hours per week; Pay Rate: $140 - $165/hour (Employee); $185 - $205/hour (Contractor)
- **Modesto/Ceres, CA:** Schedule: Weekends; Pay Rate: $140 - $165/hour (Employee); $185 - $205/hour (Contractor)

**For additional listings, please visit:**  
www.telecarecorp.com/physician-jobs/  

You will work as part of a multidisciplinary team. The staff is all very friendly and it is a supportive working environment.  
Please email your resume to Psorecruiting@telecarecorp.com

EOE M/F/V/Disability

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**Outpatient Psychiatrist Opportunity**

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

Interested J-1 and H-1B candidates are welcome to apply.  
Fax your CV to 209-468-2399 or email to BHSadministration@sjcbhs.org. EOE

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**TOP LEADING LOCUM PSYCHIATRIST SERVICES**

Please call to ask for details

**California**

- **California Correctional Facilities:** $250 Plus/hr.  
- **Department of the State Hospitals:** $280 - $290/hr.  
- **LA-DMH & LA County Jail:** $185 - $265/hr.  
- **Tulare County Adult Jail:** $200/hr.  
- **Tele-Psychiatry:** $180-$225/hr.  
- **Medical Doctors:** $150-$255/hr.  
- **NP / PA:** $65-$110/hr.

**New York**

- **Psychiatrist:** $200 - $350 Plus/hr.

**Ref. Bonus/Signing Bonus up to 2k/3k (Certain Rules Apply)**

**Free Direct Deposit**

A+ Occurrence Malpractice Through PRMS

Phone: 559. 799. 8344 Fax: 888. 712. 2412

drzuberi@psych-doctor.com

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**CHA Cambridge Health Alliance (CHA)**

Cambridge Health Alliance (CHA), a well-respected, nationally recognized and award-winning public healthcare system is seeking part-time or full-time Geriatric Psychiatrist. Our system is comprised of three hospital campuses and an integrated network of both primary and specialty outpatient care practices in Cambridge, Somerville and Boston's Metro North Region.

- Ideal opportunity for candidates interested in psychiatric care serving the local community and provide high quality care to underserved and diverse patient population.
- Fully integrated electronic medical record (EPIC) is utilized.
- Our Psychiatry service comprises of award-winning training program in Geriatric Psychiatry.
- CHA is a teaching affiliate of Harvard Medical School (HMS) 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 much more.

Candidates must be BE or BC in Psychiatry and possess strong clinical skills, commitment to public health populations and have an interest in collaborating with multi-disciplinary team.

Please visit www.CHAproviders.org to learn more and apply through our secure candidate portal. CVs may be sent directly to Melissa Kelley, CHA Provider Recruiter via email at providerrecruitment@challiance.org. CHA’s Department of Provider Recruitment may be reached by phone at (617) 665-3555 or by fax at (617) 665-3553.

We are an equal opportunity employer and all qualified applicants will receive consideration for employment without regard to race, color, religion, sex, sexual orientation, gender identity, national origin, disability status, protected veteran status, or any other characteristic protected by law.

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**NAPR**

Member of National Association of Physician Recruiters

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**Visit:** www.psychiatrictimes.com
**FLORIDA**

**UNIVERSITY OF MIAMI, DEPARTMENT OF PSYCHIATRY**

**SYLVESTER COMPREHENSIVE CANCER CENTER**

**EXCEPTIONAL PSYCHIATRY OPPORTUNITY**

Consultation-Liaison Psychiatrist

The Department of Psychiatry at the University of Miami and The Sylvester Comprehensive Cancer Center announces a search for an academic psychiatrist with interest and experience in psychosomatic medicine and psycho-oncology. Applicants can anticipate working collaboratively with fellow psycho-oncology providers including five psychologists, a psychiatrist and a team of oncology social workers.

**JOB DESCRIPTION**

Providing psychiatric consultation-liaison services in either inpatient, outpatient or both oncology settings across the oncology enterprise

Participation as a member of the Department of Psychiatry and Behavioral Sciences

Participating in teaching activity for advanced trainees to ensure the highest level of educational excellence.

**QUALIFICATIONS OF THE PSYCHIATRIST**

- Board certification in Psychiatry.
- Board eligibility/certification in C-L Psychiatry would be preferred but experience will be considered.

**COMPENSATION & BENEFITS**

This dynamic position commands an extremely competitive salary enhanced by an attractive benefits package, including but not limited to:

- Competitive compensation including bonus programs, vacation
- Comprehensive benefits include: health/dental/vision, paid malpractice, 403(b) plan

**NEW YORK**

Retiring psychiatrist seeks to pass on her general psychiatry practice for patients aged adolescent thru geriatric to a caring, experienced successor.

Located in Plainview, NY just over the Queens/Nassau border.

For information, contact: riebenjo@gmail.com

**OHIO**

Clinical Neuroscience of Mood Disorders Fellowship is looking to fill an available position.

Requirements for this position is to be a MD who has completed residency in psychiatry or related field or a PhD in Clinical Psychology. Candidate should be eligible for an Ohio Trainee License to conduct clinical work. This is a 1 - 2 year program and is accredited by the Cleveland Clinic. Position can be filled any time during the year on a rolling basis. The fellowship is designed to train fellows in clinical care and neurobiological basis of depression and bipolar disorder. Current research is focused on neurochemical, imaging and genetic biomarkers for diagnosis and treatment as well as on clinical trials of novel pharmacological agents and strategies.

Please contact Amit Anand, MD at ananda@ecf.org
With the continued growth of our Department of Psychiatry and our New General Psychiatry Residency Programs at Ocean Medical Center and Jersey Shore University Medical Center our vision for Behavioral Health is Bright.

The Department of Psychiatry at the Hackensack-Meridian Health School of Medicine at Seton Hall is seeking to recruit psychiatrists to our clinical faculty. This is a clinician-educator position (non-tenured) with both outpatient and hospital based responsibilities that can be individually defined to optimize the growth of our ideal candidates career. The position will include teaching and supervision of residents, medical students, fellows and other trainees, in a variety of clinical settings. The applicant must be a Doctor of Medicine and have completed an ACGME (Accreditation Council for Graduate Medical Education) accredited residency in Psychiatry. The applicant must possess or be eligible for an unrestricted license to practice medicine in the State of New Jersey and an unrestricted Drug Enforcement Administration license with addiction waiver. Candidate must also be Board-certified or Board-eligible in Psychiatry. Experience and interest in teaching and supervising medical students and residents in the area of is essential. We are one of the largest Psychiatry departments in New Jersey and nationally ranked with the US News and World Report. Our healthcare system includes an expanding General Psychiatry Residency Training Program and Child and Adolescent Psychiatry fellowship with emerging Addiction Medicine and Geriatric Fellowship on the horizon. We have a variety of opportunities available across the largest healthcare network in New Jersey, including Carrier Clinic, Hackensack University Medical Center and Jersey Shore University Medical Center. Our Department is remains innovative with clinical research in psychosis, anxiety and mood disorders, as well as neuromodulation which includes ECT, TMS, and Ketamine treatment.

Please visit our website at www.hackensackmeridianhealth.org/services/behavioral-health.

- Hackensack University Medical Center
- Carrier Clinic
- Riverveiw Medical Center
- Jersey Shore Univeristy Medical Center
- Raritan Bay Medical Center
- JFK Medical Center
- Ocean Medical Center

Renee.Theobald@hackensackmeridian.org or call: 732 751-3597
Novitium’s Thiothixene Capsules are offered as an affordable generic alternative to Pfizer’s Navane® Capsules, and are available in bottles of 1 mg, 2 mg, 5 mg, and 10 mg.

For more information, please visit [www.novitiumpharma.com/products](http://www.novitiumpharma.com/products)