Treating the Sickest: Why Does the US Lag Behind?

» E. Fuller Torrey, MD and Lisa Dailey, JD

Dr. Torrey is a research psychiatrist who specializes in schizophrenia and bipolar disorder. He is Founder of the Treatment Advocacy Center, Associate Director of the Stanley Medical Research Institute, and the author of American Psychosis: How the Federal Government Destroyed the Mental Illness Treatment System. Ms. Dailey is a legislative and policy counsel at the Treatment Advocacy Center. She is a lawyer and has a master’s degree in International Human Rights.

Individuals with serious mental illness who have committed major crimes pose a unique problem for balancing the clinical needs of the patient against the protection of the public. A 2011 summary of studies from 10 developed countries suggests that the US does a poor job in this task; recidivism for individuals with psychotic disorders was twice as high in the US compared with 9 other countries.1 We undertook a state survey of forensic practices to ascertain why the US does so poorly.

Treat or Repeat: A State Survey of Serious Mental Illness, Major Crimes and Community Treatment, released September 19 by the Treatment Advocacy Center, is the result.2 In the first such study, surveys and interviews were conducted with mental health and correction officials in each state to

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After Las Vegas, the Danger of Copycat Killers

Continued from cover

Yet these are probably the least useful questions to be asking now. Rather, we need to be thinking ahead to the mass-shooters-in-waiting—the copycats who will use the Las Vegas murders as a template for their own horrific schemes. And we have good reason to believe that the more publicity the Las Vegas shooter garners, the greater the motivation of copycats to “dethrone” him with the next mass shooting. (The reader will note that I do not use the Las Vegas shooter’s name in this piece).

As my colleague, forensic psychiatrist Dr. James L. Knoll IV, has pointed out, narcissism and social rejection are established risk factors for aggressive behavior. He observes that media coverage given to mass shooting perpetrators “… has sent the message that committing a spectacular act of murder or killing is a great way to get attention.”

One study by Dr. Paul Mullen examined the psychological profiles of 5 perpetrators of mass killings who were captured alive. Mullen found that, typically, these individuals were often bullied in childhood and had personality marked by suspiciousness, obsessional traits, grandiosity, and persecutory beliefs. Generally, these were individuals who intended to kill as many people as they could and then kill themselves—and they were influenced by heavily publicized cases of other mass shootings.

Only a very small percentage of gun-related killings are attributable to clinically documented mental illness. The personality profile suggested by Mullen is far too common to be of predictive value—it would yield countless “false positives” for potential mass shooters. But we can encourage more responsible media coverage of mass shootings in an effort to cut down on copycat killings.

Recently, Professors Adam Lankford and Eric Madfis have proposed 4 specific guidelines for reporting on mass killings (see Box).

Given the “Wild West” character of the internet, it may be unrealistic to expect widespread adherence to these idealistic guidelines. Yet, we must push back against the tide of media hype and perverse glamour that washes over us in the wake of mass killings. As Lankford and Madfis observe, “… by no longer publishing the names or images of mass killers, the media would stop giving them the attention they often seek, and likely deter some future perpetrators from attacking.”

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References

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FROM THE EDITOR

You Are Always on My Mind

Allan Tasman, MD | Editor in Chief

No, for a change, I’m not talking about the inundation from the 24-hour-a-day news. I’m thinking about psychotherapy and want to discuss 2 related things. The October issue of the American Journal of Psychiatry published 2 articles of major importance for those interested in strengthening the evidence base for psychotherapy.1,2 Over the past 5 decades, for a variety of reasons, the training in and availability of psychoanalytically focused psychotherapy has been diminishing. Since the publication of the Institute of Medicine’s report on evidence-based medicine, the pace of the decline has increased. Why?

In large part the decline has occurred in association with several factors related to cognitive behavioral therapy (CBT) and psychoanalysis. The first is that a large cadre of CBT faculty expertise became available in training programs to broaden the reach of teaching that modality, and at the same time psychoanalysts were leaving academia. The second factor is that the more standardized clinical approach embodied in CBT practice made outcomes research for CBT much more easily done than for psychodynamic psychotherapy research. A further factor was significant resistance from psychoanalysts—of which I’m one, so I can say this—to engage in modern outcomes research. I bemoaned this some years ago in an article I published in the Journal of the American Psychoanalytic Association, which not surprisingly to me, had little impact.

I’ve found it frustrating over the past few decades to listen to articulate CBT advocates continue to claim the superiority of CBT, based on the burgeoning research that supports its effectiveness. This occurred although there had been almost no head-to-head comparison studies. And, both forms of therapy were invented by psychoanalysts (Aaron Beck is a trained psychoanalyst, if you weren’t sure) and have the same theory of illness etiology, which is that factors outside the patient’s awareness are maladaptively influencing thinking, affect, and behavior. The theory of treatment effectiveness, though using different language to describe similar techniques and a more overtly activist therapist style in CBT, also is similar—bring the unconscious factors into awareness and work through/resolve them with the help of the therapist.

For many years, Dr. Barbara Milrod has been on the forefront of attempts to rectify the imbalance of clinical outcomes research in psychodynamic therapy compared with CBT. In her current article, she highlights the difficulties in doing a good meta-analysis, especially one that deals with psychotherapy treatment outcomes. These include ensuring not only similar diagnostic criteria and inclusion of patients across studies, but also more important for psychotherapy research, ensuring that clinical interventions are comparable within a study and across studies. Lack of such uniformity across studies has impaired high-quality meta-analytic studies analyses in many areas, but especially in psychotherapy.

It was, therefore, reassuring that her assessment of the Steinert meta-analysis was that it met a very high standard. Thus, Steinert and colleagues’ finding of essential equivalence between CBT and psychodynamic therapy was satisfying to me and many other psychodynamically inclined therapists—and was important for patient care. Milrod cites several other important studies that demonstrated positive outcomes for psychodynamic therapy, and there have been a number of others in recent years, mostly focusing on depression treatment.

The importance of the Steinert study is that it looked across diagnoses and used high inclusion standards for individual research reports. Yes, the sample sizes in the studies are small and the number of studies that could be included is small because so few met the high standard for inclusion in the meta-analysis, but this is an important contribution. And maybe this and similar reports

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A third effective mechanism for reducing the re-arrest rate is the use of Forensic Assertive Community Treatment (FACT) teams. The FACT team model for psychiatric patients in general has been in wide use since the 1970s and is highly effective. When it is used for forensic patients, a criminal justice professional is added to the treatment team. Such teams are responsible for the patients assigned to them 24/7 and also address the other needs of patients such as housing, job training, and money management. Studies of FACT teams have reported their effectiveness in significantly reducing convictions for new crimes, number of days in jail, and use of inpatient psychiatric services, compared with a control group. Yet another mechanism for reducing recidivism in individuals with serious mental illness who have committed crimes is assisted outpatient treatment (AOT). While AOT is a civil remedy, its availability relates to maintaining treatment within the community both before and after criminal justice involvement. It is available in all states except Connecticut, Maryland, and Massachusetts but is underused in most states. AOT consists of a court order that allows the person to live in the community as long as he or she follows the treatment plan. Under Kenda’s Law (New York’s version of AOT), in follow-up studies for individuals with serious mental illness who had committed any crime, recidivism was reduced by 71%. In California, where AOT is called Laura’s Law, there was a 56% reduction in recidivism and a 75% reduction in days incarcerated.

Other recommendations for improving services

Treat or Repeat identified several other ways to improve the treatment of individuals with serious mental illness who have committed major crimes. It emphasizes that these individuals are a relatively small percentage of the total psychiatric case load. Based on studies discussed in the report, at any given time there is estimated to be approximately 200,000 individuals with serious mental illness who have committed a major crime living in the community; this is just 2% of all individuals with a serious mental illness. Because of their known high rate of reoffending if they are not being treated, such individuals should be given priority for psychiatric services.

Arkansas, for example, does so explicitly on the website of the Division of Behavioral Health Services, which lists “individuals found NGRI” and “individuals committed by the courts for dangerousness to others” as the top 2 priorities for treatment. Similarly, in Missouri the state contract with the regional community mental health centers explicitly states that forensic patients are a priority population for treatment. These are models for other states.

Another way to improve the treatment of this forensic subgroup of psychiatric patients is the greater use of clozapine, the oly antipsychotic that has been demonstrated to decrease aggressive behavior. In an important 2001 article, Frankle and colleagues reported a reduction in re-arrest rates in psychotic patients with criminal histories who were treated with clozapine. Clozapine is grossly underutilized in this country compared with other developed countries, and this failure to utilize our most effective antipsychotic is another likely reason why our re-arrest rate is so high.

Finally, it is important to provide routine screening and discharge planning for seriously mentally ill individuals being released from jails and prisons. California’s mentally disordered offender designation enables screening and prioritization of services for those most in need of them in a corrections setting, including discharge planning. It is one of the only states to recognize the confluence of needs across departments, enabling enrollment of corrections inmates into its CONREP program (conditional release) and providing a model for other states to “de-silo” these 2 populations.

Ohio’s Department of Corrections utilizes a universal risk assessment tool to screen for potential dangerousness before release. Other notable corrections programs include Kentucky’s jail mental health crisis network, Kansas’ Sedgewick County Jail programming in Wichita, and Cook County’s successful discharge unit in Illinois.

Dr. Elinore McCance-Katz, the newly appointed Assistant Secretary for Mental Health and Substance Abuse, has explicitly stated that reducing the number of individuals with serious mental illness in the nation’s jails and prisons is a priority. Targeting individuals who have already been incarcerated by using programs proven to reduce recidivism is effectively going after the low-hanging fruit. Why would we not do that?

References


FROM THE EDITOR

You Are Always on My Mind

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to come will help slow the decline in the training of the next generation of clinicians in psychodynamic therapy. The reality is that other individual studies such as the Driessen study that compared CBT and psychodynamic therapy show equivalence of outcome in depression treatment. But their finding that only about 25% of patients improved with either treatment, and the fact that no one else has thus far found any formula to help a clinician determine which treatment will be more likely to succeed in any one patient, means there is still a long way to go to convince payers in the US to more appropriately reimburse for psychotherapy treatment.

The slow advances in psychotherapy research, contrasted with decades of clinician experience that support clinical improvement with...
such treatment, pertain directly to my second topic. Over the summer, The New York Times reported on a major shift in support for psychotherapy as an essential clinical intervention. Unfortunately for our patients, at least for now, this didn’t come from the US but from the UK. Their National Health Service has embarked on what the Times called “the world’s most ambitious effort to treat depression, anxiety, and other common mental illnesses.”

And how are they doing this? By essentially making unlimited psychotherapy available free of charge at clinics throughout England when the patient’s clinical condition indicates it is a necessary treatment. The goal is to eventually expand this throughout the entire UK. And, the report notes, there was widespread publicity about the initiative, including a video from Princess Harry and William talking about their own struggles after the death of their mother, Princess Diana, as well as comments from Princess Kate. The clinical head of mental health for the National Health Service is quoted as saying that the project—and its attendant publicity—has already led to a reduction in stigma among Millennials.

The program’s origins go back just over a decade, when it started on a smaller scale. Of course, the first comment we’d hear from insurers and the government about this in the US is that we can’t afford it. But given that the World Bank’s analysis of the global economic burden of all diseases will have depression at the top of the list within a few years, the predictable costs of not providing adequate treatment for all of the most common psychiatric disorders are unimaginably high—not to mention the personal and societal costs, which are much harder to quantify.

Not surprisingly, the English program has been inundated with demand, although therapy is only generally available after an appropriate clinical evaluation. Their 1-month wait time for a therapy appointment has been a cause of great concern, but they should look at the situation in the US. We don’t have very good data on wait times here because we have such a decentralized system and can’t gather it. But I think in nearly every location in the US, the wait time to begin therapy is undoubtedly much longer. I do know that yesterday I evaluated about 10 patients in our clinic and thought at least half of them would benefit from immediate therapy. Of course, they will wait much, much longer than a month to begin.

There is little chance that such an important initiative would even be seriously considered on such a grand scale in the US in the foreseeable future. Aside from the usual stigma-related discrimination against psychiatric treatments, the inability to project the cost of this type of program is a major impediment. But the experiment in the UK is gathering clinical tracking data and will at some point have direct cost data, so a cost/benefit analysis will eventually be available. I’m pretty optimistic the data will show this type of program is worth the effort not only on economic, but also on quality-of-life measures. However, much more important is that with all the therapists practicing in the US today, demand already exceeds capacity. So who would deliver all that new care?

References
Awais Aftab, MD

I am a PGY4 and Chief Resident for Education and Research at Case Western Reserve University (CWRU)/University Hospitals Cleveland Medical Center. I am an APA Leadership Fellow, and a fellow member of the APA Council of Research and have received fellowship awards from AADPRT as well as the Association of Academic Psychiatry. I have authored more than 2 dozen peer-reviewed publications and am the principal investigator for a Practice Based Research Network study investigating how the experience of psychiatric hospitalization affects trust and relationships with outpatient psychiatric providers. I’m also involved in an RCT investigating pioglitazone as a treatment for bipolar depression.

I am keenly interested in the myriad ways in which psychiatry is subject to philosophical inquiry and have developed a 6-part didactic course on the intersection of philosophy and psychiatry, which I have taught to psychiatry residents. The course covers topics such as the nature of mental disorder with regards to the debate between naturalism and normativism, the antipsychiatry movement, pluralism in psychiatry, and philosophical issues in psychiatric nosology. I am the founder and chief curator of the resident-led newsletter Research Watch, which has been featured by APA’s Ohio district branch, and received the 2017 CWRU Scholarship in Teaching award.

In my spare time, I listen to indie pop/indie rock music on Spotify, enjoy fiction and non-fiction (most recently The Stormlight Archive fantasy series and a biography of Philip K. Dick), peruse the Sunday New York Times, and binge-watch on Netflix.

Noel Amaladoss, MD

Dr. Amaladoss is Assistant Professor at McMaster University, Department of Psychiatry and Behavioral Neurosciences, and a Staff Psychiatrist at the Advanced Mind Clinic in Burlington, Ontario, whose main clinical interests are medical education, anxiety disorders, ADHD, psychopharmacology, and physician and corporate mental health. He earned his MB and ChB degrees from the University of Stellenbosch, Tygerberg Medical School, in Cape Town, South Africa, completed a psychiatry residency at Queens University in Ontario, and his fellowship at the Royal College of Physicians and Surgeons of Canada.

Kristel Carrington, MD

I grew up in Brooklyn, NY, and am of Guyanese heritage. I’ve wanted to be a doctor since the age of 3, and I fell in love with psychiatry once I got to medical school. I received excellent training at NYU and got the full expe-
rience of the diversity psychiatry offers. Now that I have completed my training, my main career goal is to be able to experience the diversity of psychiatric practice as much as possible. I do part-time work as a locum in an outpatient clinic, I have a part-time private practice, and I also moonlight in a psychiatric emergency department.

When I’m not at work, I’m usually at home relaxing with my partner and our 2 cats. I love playing video games and find them very relaxing and therapeutic—especially the first-person shooters! I also enjoy traveling, seeing natural beauty, and taking very amateur nature pics. One of my big passions is financial literacy for MDs. Doctors are horrible at managing finances, so I am big on educating early career MDs about topics such as retirement planning, safe investing, and basic budgeting.

**Ralph de Similien, MD**

I am currently a Fellow in the Public Psychiatry Fellowship at Yale University. I earned my medical degree from Wayne State University School of Medicine in 2013 and completed psychiatry residency at Howard University Hospital in 2017. I am an alumnus of Teach for America and AmeriCorps and a former elementary school teacher. My interests include public and community psychiatry, education administration, and addressing the social determinants of mental health and persistent mental illness in the transitional/college-age patient population.

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**Jessica Gold, MD, MS**

I am a fourth-year Resident and Chief in Psychiatry at Stanford University. As an undergraduate, I majored in anthropology at the University of Pennsylvania, where I was a Benjamin Franklin Scholar and graduated Phi Beta Kappa in 2009. I also received a Master’s in Science in anthropology from Penn at the same time, using qualitative methods to study premedical education for my thesis work. I received my medical degree from the Yale School of Medicine and graduated in 2014. While at Stanford, my primary interests are medical education, physician wellness, and the media portrayal of psychiatry as it relates to stigma.

I enjoy both academic and popular press writing, frequently blogging for the Huffington Post and won the 2016 Psychiatric Times essay contest for my essay, “The Mirror.” In my spare time, I spend time with my dog, friends, playing bar trivia, and my growing extended family of 7 nieces and nephews.

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**Desiree Shapiro, MD**

I am an Assistant Clinical Professor of Child and Adolescent Psychiatry at the University California, San Diego. I help patients and families in psychiatric crises on an inpatient unit, in the emergency department, and in a crisis stabilization unit at Rady Children’s Hospital. I love working on teams and with trainees to help youth and their families create a recovery plan.

I have been involved in organized medicine through the APA and AACAP and served as President of the APA Leadership Fellowship, which was an incredibly rewarding experience. I am passionate about child and adolescent psychiatry and feel fortunate to care for youth and their families. I have many interests but currently am focused on prevention and early intervention, systems of care, teaching, mentorship, and positive psychiatry.

In my spare time, I enjoy being with my 21-month-old and family. Being a mom is the hardest and greatest adventure I’ve ever had; playing with my little girl is my greatest joy! I am excited about being a part of the Editorial Advisory Board for Psychiatric Times.

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**John Torous, MD**

I am a board-certified psychiatrist and researcher at Beth Israel Deaconess Medical Center (BIDMC) and Harvard Medical School. I completed a computer sciences degree at UC Berkeley, medical school at UC San Diego, residency at BIDMC, and currently am completing a master’s degree in biomedical informatics at Harvard Medical School. My research focuses on smartphone-based passive data sensing (monitoring mobility, social, and cognitive data streams) for relapse prediction in patients with depression and schizophrenia. I’ve published over 40 peer-reviewed papers on digital technology in psychiatry. I chair the APA’s workgroup on smartphone app evaluation, advise on smartphone apps for the Precision Medicine Initiative, and co-direct the digital psychiatry program at BIDMC.

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niscence of a time not so long ago when peptic ulcer disease was considered resistant if the ulcers didn’t respond to the commonly used treatments—antacids, bland diets, and psychoanalysis (it was considered a psychosomatic disorder). The reason these interventions were largely ineffective is now understood: *Helicobacter pylori* caused most cases. Antibiotics are now the standard of care. In psychiatry, we are where ulcer treatment was a decade ago.

Currently, successful clinical outcomes are frequently the result of trial-and-error interventions, informed by limited and often anecdotal evidence. The fact is, none of the disorders covered in this report have a pharmacological treatment proven to be fully effective more often than not in most patients. One possibility is that there are multiple abnormalities in the CNS that account for the observed behavioral, emotional, and cognitive symptoms that we identify as a single disorder. The history of biological psychiatry has been marked with non-replicated claims that certain “markers” could predict treatment response.

There are also non-pharmacological causes of treatment resistance. These include noncompliance, medication intolerance, and inadequate dosage or duration of treatment. The most glaring cause of treatment failure in panic disorder that I observe is the use of benzodiazepines as needed when attacks occur. If the goal is to prevent the attacks, they should be taken on a regular schedule. In that way, the anticipatory anxiety and phobic avoidance can be slowly resolved. In ADHD, treatment often fails because the effects of even long-acting drugs tend to wear off by late afternoon. In the case of bipolar disorder, patients often discontinue their medication, deliberately or irresponsibly, and quickly lose insight into their emerging change of mood.

It is often said that psychopharmacology involves the art of using medications appropriately as well as the intrinsic effectiveness of the medications themselves. Hopefully, the information contained in this report will help clinicians improve treatment outcomes in some of the most challenging patients we encounter.

Dr. Sussman reports no conflicts of interest concerning the subject matter of this Special Report.

Reference

Treatment-Resistant PTSD

Dr. Koek is Staff Psychiatrist at the Sepulveda Ambulatory Care Center, VA Greater Los Angeles Healthcare System; Director of the Mood Disorders Clinic, UCLA/San Fernando Psychiatry Training Program; Clinical Professor, Department of Psychiatry and Bio-behavioral Sciences at the David Geffen School of Medicine at UCLA in Los Angeles; and Teaching Faculty at the Family Medicine Residency Program, Glendale Adventist Medical Center in Glendale, CA.

Treatment-resistant depression has been discussed widely for years, but treatment resistance in PTSD—another common, serious, disabling condition—has been less frequently addressed in the literature. While 70% of the world’s population has been exposed to a traumatic event, only 5.6% meet DSM-5 criteria for PTSD. Moreover, 44% of patients with a PTSD diagnosis recover even without specific treatment.

Trauma-focused cognitive-behavioral therapy (TF-CBT), such as prolonged exposure therapy, cognitive-processing therapy, or eye movement desensitization and reprocessing, has been recommended as first-choice treatment for chronic PTSD. TF-CBT and non–trauma-focused CBT may be equally effective post-treatment; TF-CBT has been found to be more effective at 1 to 4 months’ follow-up. However, there is a high dropout rate from these treatments. Two-thirds of veterans who complete cognitive-processing therapy or prolonged exposure therapy retain a PTSD diagnosis despite large within-group effect sizes; significant sleep problems often persist, and there are less data about longer-term follow-up.

<table>
<thead>
<tr>
<th>TABLE 1. Assessment and management of treatment-resistant PTSD</th>
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<tr>
<td><strong>Factor</strong></td>
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<tr>
<td>Allow natural recovery: resilience is important, varies between individuals, and can lead to recovery without specific intervention</td>
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<tr>
<td>Provide support with evidence-based intervention</td>
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<tr>
<td>Provide sufficient treatment duration</td>
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<tr>
<td>Address comorbidity</td>
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<tr>
<td>Address sleep disturbance: lack of improvement in sleep predicts poor PTSD treatment outcome; nightmares and associated dysfunctional REM sleep can impair processing of other aspects of PTSD and affect outcome</td>
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<tr>
<td>Identify most salient symptom cluster(s) based on DSM-5 criteria</td>
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<tr>
<td>Identify subtypes</td>
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<td>Consider trauma severity</td>
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<tr>
<td>Consider trauma type</td>
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<td>Address specific psychological factors</td>
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**CASE VIGNETTES**

Ms. A, 55 years old, has had depression, panic attacks, insomnia, and social withdrawal that have not benefited from trials of citalopram, paroxetine, and sertraline over the past 3 years. At intake, she describes persistent grief for the past 10 years since witnessing the shooting death of her son. She is unable to describe the incident, exhibits the conviction that she is responsible for the death, and has difficulty acknowledging that her child is gone. She persistently re-experiences the traumatic event with a mixture of sadness, anger, and guilt. Her anxiety consists of extreme social avoidance and hypervigilance, and she has frequent nightmares.

Mr. B is a 66-year-old Vietnam combat veteran. Over the nearly 40 years since the Vietnam War, he has been able to work in an administrative position and raise a family, without substance use disorder, serious general medical conditions, or legal problems. On the other hand, besides his work and involvement in a Veterans Service Organization, he has engaged in little social activity with his family or otherwise—no concerts, ballgames, movies, holiday parties, etc. He has undergone multiple unsuccessful pharmacology trials. At presentation, he is taking 200 mg of sertraline and 2500 mg of divalproex daily, and 4 mg of clonazepam and 500 mg of quetiapine daily at bedtime. He has persistent insomnia, severe combat nightmares, angry hyperarousal, and hypervigilance.

**TREATMENT RESISTANCE**

**Treatment nonresponse**

Only 2 medications have FDA indications for PTSD: paroxetine and sertraline. Some treatment guidelines recommend these or other antidepressants, including fluoxetine and (CONTINUED ON PAGE 18)
Treatment-Resistant PTSD

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venlafaxine, as equivalently first choice with focused CBT. Others regard focused CBT as having better evidence and suggest antidepressants only when therapy has failed or is not available, or in cases of severe depression. This reflects a number of negative randomized clinical trials (RCTs) with SSRIs, and small-to-moderate effect sizes relative to TF-CBT.

Many patients remain symptomatic and functionally impaired despite standard treatments and require alternative interventions. In a review of the pertinent literature on treatment-resistant PTSD, it was found that only 53% of 167 RCTs, open-label studies, and case series that assessed the efficacy of medication other than sertraline or paroxetine described failure of prior pharmacotherapies, and only 3% described failure of TF-CBT. The only RCT of an SSR (paroxetine) in CBT non-responders failed to show benefit. Systematic investigation of CBT in pharmacotherapy non-responders has also received little investigation. The complexity of the literature did not permit specific recommendations about relative benefits of alternative next-step pharmacologic strategies in paroxetine/sertraline non-responders.

Recommendations for second-line pharmacotherapy vary widely among recent reviews and treatment guidelines with a second antidepressant most often recommended for initial treatment failures. Despite a large, negative 6-month multicerter RCT of risperidone augmentation of antidepressants, some—but not all—treatment guidelines recommend atypical antipsychotic augmentation when antidepressants fail. None recommend atypical antipsychotic monotherapy or typical antipsychotics. Most specifically mention prazosin: one guideline recommends it in conjunction with focused CBT as the best initial treatment, while others recommend it as a second-line treatment.

Most experts agree that patients with PTSD and persistent nightmares should not be regarded as treatment refractory unless they have had an adequate trial of prazosin, which should be a minimum of 10 mg daily at bedtime, with additional daytime dosing in some patients. Prazosin may require careful titration over several months. Anticonvulsants are not supported by strong evidence, although some found the evidence for topiramate more convincing than others. I have seen benefit in some patients who have nightmares, although adverse effects are common.

One notable finding—unfortunately unchanged since Hamner and colleagues made the same observation in 2004—is that there is a dearth of evidence on lithium in PTSD, including no RCTs. This is unfortunate given associations between PTSD and suicidal behavior, anger dyscontrol, and impulsivity, which are potential targets for long-term lithium therapy. In my experience, both individuals with clear bipolar comorbidity and patients in whom bipolar NOS is more difficult to separate from severe PTSD may benefit.

Burrolase has been used as an augmentation strategy to enhance extinction in conjunction with exposure, with largely unimpressive, although complex, results. To date, it has not demonstrated efficacy in treatment-resistant PTSD.

Dunlop and colleagues developed the Emory Treatment Resistance Interview for PTSD (E-TRIP). It does not provide an algorithm for next-step treatment but allows the clinician to generate a numerical score for degree of treatment resistance in an individual based on failure of pharmacotherapies and psychotherapies, with RCT data supporting efficacy.

Table 1 addresses some of the complexities in assessing and managing treatment-resistant PTSD. The Case Vignette also illustrates some of these points. Ms. A’s treatment consisted of psychoeducation about the nature of PTSD followed by prolonged exposure, as well as extensive cognitive-processing therapy that addressed “survivor guilt.” After nearly 2 years, she came to accept her child’s death; recovered from her self-blame; and her depression, hypervigilance, and avoidance improved. Sleep improved with trazodone once her avoidance and hypervigilance responded to exposure. Venlafaxine, 225 mg daily, provided more benefit than SSRIs.

Mr. B required systematic medication changes over 2 years, with a final regimen of 15 mg of prazosin and 30 mg of mirtazapine daily at bedtime plus 300 mg of sertraline and 50 µg of levothyroxine sodium daily (based on exacerbations of comorbid anergic depression correlated with normal thyroid-stimulating hormone levels of 3.5 to 4.5 µIU/L from a baseline of 1 to 2.4 µIU/L). With this regimen, nightmares stopped and he slept 7 to 8 hours for the first time in decades. The improvement in sleep and depression permitted in vivo exposure therapy that reduced first avoidance behavior and secondarily anger and hypervigilance. He has remained essentially well now for more than 3 years, even with current doses of 200 mg of sertraline, 15 mg of mirtazapine, and 5 mg of prazosin.

Specific etiology

PTSD is relatively unique among psychiatric disorders in requiring a specific etiology. Treatment must first address the specific individualized aspects of the trauma itself and contextualize its role in the patient’s life. Certain types of trauma can reduce the likelihood of spontaneous recovery (eg, PTSD due to medical illness) or response to treatment: childhood abuse-related trauma, repeated or prolonged trauma, more severe trauma, and trauma associated with marked impairment of self-regulation. Combat PTSD is frequently regarded as less responsive to standard treatments than single-event trauma.
There is no “best” evidence-based treatment for all patients, and this is true for treatment-resistant PTSD. Pharmacologic management must be individualized, and the use of focused CBT in conjunction with pharmacotherapy may require careful, flexible integration, sometimes across months or years of treatment—as in Ms. A’s and Mr. B’s cases. Still, as also illustrated by Mr. B’s case, empirical data summarized in Tables 2 and 3 may be of value in making medication changes.

There are medications with expert recommendations against their use (benzodiazepines), with uniformly negative RCTs (divalproex, bupropion, guanfacine, tiagabine), or with a mixture of both positive and negative evidence (fluoxetine, mirtazapine, risperidone, olanzapine) augmentation of antidepressants, topiramate). Furthermore, some commonly used pharmacologic agents have not been subject to RCTs in PTSD (citalopram, escitalopram, gabapentin, clonidine, lidocaine), nor have many newer agents such as levomilnacipran, milnacipran, amitriptyline, and bupropion. Given the challenges in helping people with treatment-resistant PTSD, it was not surprising to find an impressive variety of alternative pharmacologic agents that have shown benefit in at least some treatment-resistant patients (Table 3). Future research may lead to agents that directly address neuropharmacologic mechanisms of extinction in the amygdala including glutamate/NMDA modulators.48

While RCTs of medications typically involve weekly to bimonthly follow-up visits, and prolonged exposure therapy and cognitive-processing therapy require weekly visits for standard implementation, for many patients, such frequency of visits is limited by practical considerations (eg, cost, work obligations). This was true for Ms. A and Mr. B. For many patients like Ms. A and Mr. B, who have suffered for years, it may not be surprising to find that medication changes may take months or longer to achieve optimal benefit, and some components of focused CBT involve changes in maladaptive habits, ingrained after trauma, that take time to implement.

It is important to note that the author reports no conflicts of interest concerning the subject matter of this article.

References

### TABLE 3. Open-label investigations in patients described as refractory to other treatmentsa

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<thead>
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<th>Pharmacologic Category</th>
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<th>OLI- (N)</th>
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<td>Antidepressants</td>
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<td>Mirtazapine</td>
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<td>Nefazodone</td>
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<tr>
<td>Antipsychotics</td>
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<tr>
<td>Quetiapine</td>
<td>87</td>
<td>32</td>
</tr>
<tr>
<td>Risperidone</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td></td>
<td></td>
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<tr>
<td>Carbamazepine</td>
<td>18</td>
<td></td>
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<tr>
<td>Divalproex</td>
<td>37</td>
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</tr>
<tr>
<td>Levetiracetam</td>
<td>23</td>
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<tr>
<td>Pregabalin</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Tiagabine</td>
<td>7</td>
<td></td>
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<tr>
<td>Antidepressive agents</td>
<td></td>
<td></td>
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<tr>
<td>Clonidine</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Prazosin</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buspironne</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Triiodothyronine</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Tetrahydrocannabinol</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Creatine monohydrate</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Nafrineoxide</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Sodium picolaminate</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Tramadol</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

*aOpen-label investigations (OLIs) showing improved PTSD symptoms in patients unresponsive to paroxetine or sertraline.

*bOpen-label investigations showing lack of improvement in PTSD symptoms in patients unresponsive to paroxetine or sertraline.

TREATMENT RESISTANCE
be routinely offered. In a large, placebo-controlled, multisite, comparative PD treatment study of CBT (with interoceptive desensitization) plus imipramine versus monotherapies, combination treatment effects were superior at the end of 12 weeks. Although the patient has a diagnosis of TRP, the goal of treatment is still to achieve a remission state, as this protects against relapse and lowers the risk of complications.

Genetic testing may be of value if the patient has been intolerant of or resistant to several standard-of-care medication trials. Findings suggest that patients (especially females) with 5-HT transporter promoter gene short (s) alleles, are less likely to respond to SSRI treatment. Moreover, patients who are “slow metabolizers” may respond to modest doses of standard agents and require a slower upward titration schedule. 

### TABLE 2. Suggested augmentation medications for SSRI/SNRI-resistant PD

<table>
<thead>
<tr>
<th>Medication class</th>
<th>Specific medication</th>
<th>Daily dose range</th>
<th>Putative anxiolytic mechanism</th>
<th>Preparations</th>
<th>Clinical comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepine full agonists</td>
<td>Clonazepam</td>
<td>0.25 - 4 mg</td>
<td>Positive allosteric modulation at GABA, receptor complex</td>
<td>Tablet, ODT (swallowing difficulties/fear of choking an issue for PD patients)</td>
<td>Daily or BID dosing; monitor cognition; addiction risk limited by regular follow-up/monitoring</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>0.5 - 6 mg</td>
<td>As above</td>
<td>Tablet, ODT, IR, and ER formulations</td>
<td>Daily dosing possible with ER formulation</td>
<td></td>
</tr>
<tr>
<td>Lorazepam</td>
<td>0.5 - 8 mg</td>
<td>As above</td>
<td>Tablet, IM, IV</td>
<td>TID or QID dosing</td>
<td></td>
</tr>
<tr>
<td>Atypical antidepressants</td>
<td>Mirtazapine</td>
<td>15 - 45 mg</td>
<td>Antagonizes 5-HT2A, 5-HT2C, 5-HT3, and H1 receptors</td>
<td>Tablet, ODT</td>
<td>HS dosing; sedative effects useful for insomnia; few controlled studies in PD; weight gain risk</td>
</tr>
<tr>
<td>Bupropion</td>
<td>75 - 300 mg</td>
<td>NE/DA reuptake inhibitor</td>
<td>Tablet, IR, SR, and ER formulations</td>
<td>Use cautiously; may help limit AEs, and address MDD comorbidity; caveat: agitation risk</td>
<td></td>
</tr>
<tr>
<td>Azapirones</td>
<td>Buspirone</td>
<td>10 - 30 mg/d</td>
<td>5-HT1A partial agonist</td>
<td>Tablet</td>
<td>FDA approved for “anxiety”; could treat comorbid GAD or MDD; caveat: the 1-PP metabolite is an α-2 adrenoreceptor antagonist, which could increase anxiety; BID or TID dosing</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Gabapentin</td>
<td>100 - 900 mg</td>
<td>Binds to voltage-sensitive calcium channels; indirect GABA enhancer</td>
<td>Capsule, tablet, ER tab, liquid</td>
<td>Good adjunctive agent, weak monotherapy; HS or BID dosing feasible; low cost</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>150 - 450 mg</td>
<td>As above</td>
<td>Capsule</td>
<td>More potent, more costly than gabapentin; approved in the EU for GAD</td>
<td></td>
</tr>
<tr>
<td>Valproic acid</td>
<td>250 - 1000 mg</td>
<td>GABA enhancer</td>
<td>Tablets, ER tablet, capsules, syrup</td>
<td>Lab monitoring needed; monitor for weight and sedative/cognitive AEs; may be good option for patients with comorbid bipolar disorder</td>
<td></td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>50 - 100 mg</td>
<td>Inhibits glutamate release</td>
<td>Tablet, ODT, chewable tab, ER tab</td>
<td>High likelihood of benign rash; otherwise fairly well tolerated</td>
<td></td>
</tr>
<tr>
<td>Atypical antipsychotics</td>
<td>Risperidone</td>
<td>0.5 - 2 mg</td>
<td>Postsynaptic 5-HT2A/2C antagonism; promotes anxiolysis</td>
<td>Tablet, ODT</td>
<td>Postsynaptic 5-HT2A/2C effect is more active at lower doses; RCT data in PD/bipolar patients</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>2.5 - 10 mg</td>
<td>As above</td>
<td>Tablet, ODT</td>
<td>Weight gain and sedation common; promising augmenter in a smaller GAD RCT</td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td>50 - 200 mg</td>
<td>As above</td>
<td>Tablets: IR and ER formulations</td>
<td>Positive monotherapy multisite RCT in GAD</td>
<td></td>
</tr>
</tbody>
</table>

*PD, panic disorder; ODT, orally disintegrating tablet; IR, immediate-release; ER, extended-release; 5-HT, serotonin; NE, norepinephrine; DA, dopamine; AE, adverse effect; GAD, generalized anxiety disorder; RCT, randomized controlled trial.*
and the slight risk of benzodiazepine abuse/diversion, especially with longer-term use. In fact, benzodiazepines are similarly effective to antidepressants for panic disorder, and their panico-lytic benefit is almost always sustained over the long term.

Adverse effects such as sedation and incoordination are most apparent in the initial weeks of therapy, and this is when the risks for operating heavy machinery and driving are elevated. Thereafter, tolerance to the sedative effects occurs.

Benzodiazepines may have a long-term tolerability edge over the SSRI s, SNRIs, and TCAs, as they do not cause weight gain or sexual dysfunction. Generally, high-potency, shorter half-life benzodiazepines are preferable because of their more predictable pharmacokinetics and simpler metabolism. Regular dosing (vs PRN) is recommended to achieve optimal anxiolyysis. In considering the rationale for long-term benzodiazepine administration, review the Dunport criteria clinical probes listed in Table 1. For additional details on dosing and administration, see Table 2.

The concern that benzodiazepines disrupt the effectiveness of evidence-based psychotherapies for panic, such as CBT, has not been confirmed in recent anxiety clinical trials.

Augmentation strategies (Table 2) is a meta-analysis of controlled studies in resistant anxiety disorders demonstrating limited additional benefits with several augmenting strategies (benzodiazepine, atypical antipsychotic, or pregabalin). The second step of the study from Simon and colleagues’ included random assignment to either clonazepam or CBT. These options were similarly effective next-step interventions. Accordingly, coadmin-istration of a benzodiazepine is a reasonable first-choice augmentation option and is safe for long-term treatment. If this is not effective or tolerated, coadministration with an atypical an-tildepresant, such as mirtazapine, is a reasonable second step. A suggested third step in augmentation is addition of an anticonvulsant agent (e.g., gabapentin, pregabalin, valproic acid, lamotrigine), as data from meta-analyses provide some support for this practice in anxiety and PD, and even suggest the potential benefit of an EEG in the work-up for TRP patients to improve anticonvulsant outcomes. Finally, while a positive evidence base for second-generation antipsychotics in PD and TRP is limited, current reports suggest that low-dose coadministration or monootherapy is tolerated in short-term trials. Recognized compared with other high-prevalence refractory conditions, such as treatment-resistant depression. There has been debate about the criteria for resistance, but failure of optimal treatment (attainment of remis-sion) at 2 evidence-based interventions over a 6-month period, is a useful clinical definition. One measurement-based approach to TRP recognition involves the use of the collaborative panic disorder severity scale (PDSS). In general, the goal of clinical treatment of PD is to achieve a remission state (PDSS total score of 4 or lower). TRP should be treated vigorously with this goal in mind, as residual symptoms confer a higher risk of clinical complications.

While few controlled treatment studies inform monotherapy, combination treatment, and augmentation approaches for TRP, clinical guidelines, treatment meta-analyses, and expert opinion offer some guidance. On occasion, special tests such as EEG or genetic testing may be indicated and can contribute to better outcomes. Currently, a range of interventions (phar-maco-therapies, psychotherapies, and complementary and neuromodulation interventions) offer hope and help for patients. However, in the future, personalized medicine strategies, involving baseline genotyping and functional neuroimaging, will be offered in a more predictive approach to TRP care planning.

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References

Borderline Personality Disorder: Treatment Resistance Reconsidered

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The concept of treatment resistance deserves reconsideration. Originally formulated in psychoanalytic terms, resistance in treatment referred to the inevitable ways patients unconsciously express their psychology in terms of defense mechanisms and transference enactment. This form of resistance provides a window into the patient’s problems; therefore, it is a major focus of the inquiry and intervention. Modern psychiatry defines treatment resistance as a lack of response to adequate treatment. Both conceptualizations locate treatment resistance within the patient, rather than as a product of limited, underdeveloped, and ineffective treatments. As a result, the term “treatment resistant” can fuel views of patients as “oppositional” and recalcitrant, instead of expectably symptomatic.

Treatment resistance is highly prevalent across most psychiatric disorders—even in common diagnoses generally associated with positive outcomes, such as depression. There are many more obstacles to effective treatment (Figure 1) than the patient’s psychological resistance alone. Identification of specific factors that diminish treatment response may provide more useful points of intervention than the label of treatment resistance.

Comorbid disorders contribute to poor treatment response. Treatment guidelines are often based on a false assumption that patients present with single disorders that respond to specific evidence-based treatments. Regardless of increasing attention to problems of comorbidity, guidelines for combining and prioritizing the treatment of different diagnoses remain largely underdeveloped.

Comorbid personality disorders complicate treatment. Over 50% of patients in specialized psychiatric settings have personality disorders. These patients are more likely to face social adversity, suffer from complex comorbidities, and drop out of treatment or not adhere to medication regimens—all of which contribute to an increased risk of a lack of response to treatment. The presence of a personality disorder, particularly borderline, predicts persistence of anxiety and substance use disorders as well as poorer outcomes in depressive disorders. Moreover, 13% of those who complete suicide have personality disorders.

Clinicians often see patients with personality disorders as treatment resistant—and, in some cases, untreatable.1 While it is true that patients with personality disorders may be challenging to treat, they are treatable. The self-defeating coping skills and difficulty with relationships that are central to personality disorders make a productive treatment alliance difficult to sustain. Clinicians prototypically react with feelings of frustration, disengagement, incompetence, confusion, helplessness, and even rage. The identification of these countertransference reactions can facilitate the diagnosis of personality disorders but can overwhelm and disturb clinicians, leading them to avoid diagnosis and personalize problems as a product of either the patient’s immutable character or the clinician’s limitations.

Our progress in understanding and treating borderline personality disorder (BPD) illustrates the benefits of centralizing the personality disorder diagnosis in care management. For over half a century, patients with BPD were identified by their negative therapeutic reactions, that is, worsening with what was thought to be otherwise appropriate treatment. While pessimism and stigma about the disorder remain, our notion of BPD’s prognosis has radically improved with research.

A major longitudinal study of BPD and other personality disorders with 16 years of follow-up showed that virtually all subjects with BPD achieve sustained remission for at least 2 years, and 78% sustain remission for 8 years. Recovery, that is attending work or school and sustaining at least one meaningful relationship, occurred for 60% of patients for 2 years, and was maintained in 40% over 8 years.1 This evidence suggests that the majority of individuals with BPD (and other personality disorders) can achieve remission and most can recover some sustained functioning, which challenges the notion that patients themselves resist treatment.

Research findings also demonstrate that BPD responds to a variety of treatments. Several specialized psychotherapies formulated for BPD—dialectical behavior therapy (DBT), mentalization-based treat-
ment (MBT), schema-focused psychotherapy, and transference-focused psychotherapy (TFP)—reduce self-injury, suicide attempts, and hospitalizations. These gains remain 3 years after the beginning of treatment.

Although the results are positive for long-term treatment effectiveness for BPD, difficulty in learning and implementing these psychotherapies because of their specialization and intensity renders them largely unavailable to most patients and clinicians. The difficulty in providing or referring patients to effective care is therefore a major factor in treatment resistance and challenges to treating BPD.

A recent meta-analysis of evidence-based psychotherapies for BPD suggests that structure and focus on BPD-related problems such as self-harm and suicidality, rather than intensity, determine outcomes. The small-to-medium effect sizes related to the efficacy of evidence-based therapies disappear in studies where the control treatment is structured. Intensity (ie, duration and exposure) did not appear to influence outcomes.

This meta-analysis did not show significant differences between DBT and psychodynamic approaches (which included MBT and TFP). It also reported that cognitive behavioral therapy performed no better than control conditions, which indicates that structured treatment alone is not sufficient; the treatment needs to focus on BPD. These findings suggest that evidence-based treatments might be simplified and still retain effectiveness by maintaining structure and specificity for BPD patients.

The findings from 2 large outpatient trials of DBT and MBT support the idea that less intensive but structured, informed, and systematic care of BPD patients can be effective. General Psychiatric Management (GPM) and Structured Clinical Management were compared with outpatient DBT and MBT, respectively. Both specialized and generalist approaches yielded similar decreases in suicidality and non-suicidal self-injury and improvements in interpersonal functioning and quality of life. While further research is needed, these findings suggest that treatment resistance can be overcome with informed and structured care. We propose the following strategies.

**Diagnosis and psychoeducation**

Good care for BPD begins with a diagnosis. Many clinicians avoid telling patients, particularly adolescents, that they have a personality disorder. But the BPD diagnosis can be made reliably before the age of 18, and early intervention is needed for better outcomes. When the diagnosis is made objectively and optimistically, patients typically feel less alienated and alone, as well as more hopeful. Sitting down with a patient to review the diagnostic criteria for BPD is an opportunity for clinicians and patients to think together about how each criterion can be applied to challenges the patient faces.

It is important to inform patients that social and vocational recovery is more difficult to achieve than symptom remission alone. These challenges and their course of treatment can be delivered in a clinical management approach that is not primarily psychotherapeutic. An essential part of this is to explain that difficulties in the clinical relationship are to be expected. This allows both patient and clinician to manage these disruptions, rather than react in overly personalized or pejorative ways.

The clarification of treatment goals and expectations, as well as predictions about therapeutic challenges, functions primarily to educate the patient. Psychoeducation alone can reduce symptoms of interpersonal instability and impulsivity. With a shared understanding of how interpersonal and emotional sensitivities connect to self-destructive tendencies (ie, self-harm or suicide attempts), the patient and clinician can communicate and collaborate around symptom management in a consistent way.

**Management of suicidality and self-harm**

Evidence-based treatments for BPD stabilize high-intensity interchanges between self-destructive patients and their clinicians by providing an established framework for managing self-destructive behaviors. Good clinical management of any psychiatric diagnosis guides mental health professionals to establish a plan that patients can use when they have urges to hurt themselves at the beginning of treatment. When self-destructive problems arise, patients then have resources mapped out so that independent management can increasingly replace reflexive reliance on hospitalization or paging. According to GPM, clinicians can actively evaluate suicide risk by weighing risk factors (eg, prior attempts, access to means, dangerousness of plans, assessment of intent, substance use, and depression) against protective factors (eg, social supports, capacity to use skills and entertain alternatives). After these episodes, clinicians and patients can analyze what is working in the safety plan and what needs modification.

Chain analyses, reviews of the various events and internal reactions leading to self-destructive urges, are used in many evidence-based treatments for BPD. The chain analysis helps clinicians and patients to better understand what has happened and revise safety plans accordingly. With a shared system of managing safety and a shared expectation that reducing suicidality and self-harm is a focus of treatment, more treatment collaboration rather than resistance occurs.

**Management of comorbidities**

BPD rarely presents without major comorbidity. Most patients with BPD also suffer from depression and anxiety disorders, and many have problems with substance use, eating, and other personality disorders. However, useful and scientifically informed guidelines for prioritizing focus on BPD over other comorbidities are provided in GPM (Figure 2). These guidelines encourage clinicians to prioritize BPD over its most common comorbidities of depression, panic disorder, generalized anxiety, and other personality disorders, because these comorbidities are less likely to remit if BPD symptoms do not improve. Moreover, randomized controlled trials of existing evidence-based treatments for BPD report concomitant reductions in depression and anxiety during and after treatment.

Other comorbidities, such as substance dependence, anorexia, and mania, must be prioritized over BPD treatments, because these disorders interfere with the learning required in BPD treatment. New evidence indicates that BPD and PTSD can be treated effectively at the same time. PTSD symptoms may even improve with the treatment of BPD alone.

These empirically informed guidelines mitigate the chaos and reactivity that challenge clinicians in their management of multiple comorbidities by providing an organizational framework. Improving BPD by enhancing coping and interpersonal functioning is likely to increase self-regulation and the sustainability of supportive relationships, while decreasing stressors. Informed management of comorbidities with BPD can reduce treatment resistance, with a focus on a central and treatable source of vulnerability and dysfunction.

**Conservative prescribing of pharmacological and somatic therapies**

No medication is FDA-approved for the treatment of BPD. Few randomized controlled trials have tested pharmacological treatments for BPD, and their results are inconclusive. European guidelines from the National Institute for Clinical Excellence state that existing evidence is insufficient to support any prescribing of medications, except for the treatment of diagnosable comorbidities. American Psychiatric Association guidelines, informed by meta-analysis of the small number of existing pharmacology studies, advocate for judicious use of mood stabilizers and antipsychotics for BPD symptoms related to affective instability, impulsivity, and cognitive perceptual symptoms.

Antidepressants show minimal benefit in the treatment of core BPD features. Similarly, BPD patients respond to ECT inconsistently, with lower degrees of antidepressant re-
Bulimia nervosa (BN) is a serious disorder characterized by recurrent large-volume eating episodes that are marked by a loss of control (binge eating), regular compensatory behaviors that are intended to prevent weight gain (purging), and over-valuation of body shape and weight. BN is associated with psychiatric comorbidity, significant psychosocial impairment, medical complications, and increased mortality.

Clinical guidelines for the evidence-based treatment of BN highlight first-line, outpatient psychotherapeutic and pharmacological approaches. Self-help, enhanced cognitive-behavioral therapy (CBT), and interpersonal psychotherapy are considered first-line psychotherapeutic interventions. Antidepressants, most notably SSRIs and specifically fluoxetine, which is FDA-approved for use in BN, are recommended adjunctive first-line treatments. Limited data suggest that CBT-BN alone and CBT-BN plus antidepressants are more efficacious than antidepressants alone.1 Despite these available treatment options, roughly 30% of cases are chronic and unremitting. Even for those who do initially respond to treatment, estimated rates of relapse in BN range from 25% to 63%.2

CASE VIGNETTE

Melia is a patient with treatment-refractory, complex BN, who presents for treatment at our eating disorders program. A 20-year-old college student, she plans to attend law school after graduation. Her eating disorder began in her freshman year, when she started “using food to cope” after a difficult breakup and domestic violence. Before admission, she was eating salads or diet frozen entrées for most meals and binge eating and purging 3 to 5 times a day. She has a history of self-harming behaviors and 2 suicide attempts. She reports frequent shoplifting, occasional binge drinking to the point of blacking out, and recurrent unsafe sex with men she meets at bars. She previously had attempted outpatient, partial hospital, and residential treatment but had been unable to sustain recovery. She also had several trials of antidepressant medication without response for depression, anxiety, and eating-disordered symptoms.

Melia reports that she feels “very stressed” at school and has high standards for herself. She has had to withdraw from school several times to pursue treatment. Improving outcomes for individuals with treatment-resistant BN such as Melia hinges on: 1) Developing an understanding of what factors make treatment failure or dropout more likely, 2) Generating hypotheses about the mechanisms of non-response, and 3) Proposing and evaluating treatments that address these hypothesized mechanisms.

Factors underlying treatment failure

In general, first-line psychotherapeutic treatments—whether delivered in person or via telemedicine—result in remission in only 30% to 50% of adult patients with BN.3 These first-line treatments are often particularly ineffective for the large subset of patients who struggle with a range of other dysregulated behaviors. To date, despite some inconsistency in the literature, predictors of worse outcome or treatment dropout include longer duration and more severe BN symptomatology, comorbidity, and character-istics of personality pathology.15 These psychotherapeutic approaches focus on skills and strategies to stabilize the expectable challenges and thereby reduces treatment resistance overall. The authors report no conflicts of interest concerning the subject matter of this article.

SIGNIFICANCE FOR THE PRACTICING PSYCHIATRIST

Bulimia nervosa can be a treatment-refractory condition; rates of relapse range from 25% to 63%. Predictors of worse outcome or treatment dropout include longer duration and more severe eating disorder symptom profiles, comorbid psychopathology, and characteristics of personality pathology. Treatment approaches focus on skills and strategies designed to help patients regulate emotions and cope with altered inhibitory control and reward sensitivity. Dialectical behavior therapy may be particularly effective in mitigating biologically driven vulnerabilities to unstable affect and maladaptive, impulsive behaviors. Recently, a few encouraging but very small open series and case reports have been published on zonisamide and lamotrigine. The use of evidence-based treatment protocols to target comorbidities is also essential, although complicated questions remain about how to integrate treatments.

REFERENCES

he uncanny eludes facile definition. Savants diverse as Nietzsche, Poe, Freud, and Jung have had a go at those mysterious creeps that prick up your hair and unsettle your mind. However trenchant, speculations about the nature and causes of the uncanny somehow end up wide of the mark.

At base, uncanny experiences are rooted in the realm of the unconscious—individual or collective (if your bent is Jungian). And the workings of the unconscious sui generis refuse tidy explanation because they’re recoverable only in conscious “traces”—eerie moments of déjà vu, slips of the tongue, and in the waking residue of our dreams.

In high or popular art, the uncanny customarily summons up midnight graveyards, unquiet ghosts, doppelgangers, the living dead. Freud’s famous essay, Das Unheimliche, (1919) itself possesses an uncanny cast: his usually incisive prose is strangely prolix; his speculations uncharacteristically equivocal.

Freud cites several examples of the uncanny in literature—eg, Olympia, the exquisite mechanical simulacrum of a human ballerina, in E.T.A. Hoffmann’s The Sandman. He goes on to posit an intimate relationship between the comfortable (heimlich) feelings related to ordinary things and events, and the uncomfortable, even dreadful (unheimlich) sensations the same objects and events generate. These may occur in stressful circumstances, but sometimes emerge unbidden, ex nihilo.

Freud theorizes that unheimlich perceptions are precipitated by the activation of repressed childhood “complexes,” oedipal, pre-oedipal, so forth. I’ve found little clinical evidence to back up this speculation. But I do believe that horror fiction, painting, and cinema are often most frightening when quotidian reality gives way to a vastly troubling perception that the real world comprises a thin scrim, overlaying a rich, numinous, and often terrifying underworld.

Stephen King is today’s foremost adventurer into that unheimlich nether region. King is astonishingly prolific. He has published at least 50 novels and 200 short stories in the horror/sci fi genres. He has also written children’s books, policies, and private eye mysteries, an autobiography, and diverse essays—one of the best on the vicissitudes of writing.

King’s genre work ranges across the broadest spectrum of the horrific and uncanny. He has borrowed honorably from masters like Poe and Bram Stoker; repurposed classic inhabitants of monster alley like Dracula (and Salem’s Lot, 1975), and created his own creatures of the night, including a shapeshifting satanic clown—of which more presently.

He has probed virtually every parapsychic phenomenon—eg, precognition, in The Dead Zone (1983). The heimlich/unheimlich trope often figures prominently in his oeuvre, eg, the gleaming roadster, come murderous alive in Christine (1983).

King has always drawn abundantly from his own childhood and adult experiences. Abandoned at age 2 by a merchant marine father, he was raised by his working-class mother under harsh circumstances, mostly in a small Maine town. The Maine hamlet of “Derry” is its replication, and frequently appears in the nether.

King is singularly adept at capturing the vicissitudes, mores, and speech of pre-teenagers (particularly boys) throughout his writing—most notably in one of his longest novels, IT (1986). Adapted for an uninspired television miniseries in 1990, IT has been re-adapted again for the screen. As I write, the current film remains immensely popular and has generated blockbuster box-offices across the world.

IT is set in Derry. The town and its verdant countryside first appear Grand- ma Moses’ heimlich. Everybody knows everybody, Derry people seem folksy enough—if sometimes given to gossip, and a bit quick to make hurtful judgment. But a wave of child disappearances is afflicting the town, not for the first time. And the facade of the tidy houses can conceal cruel, perverse deeds, perpetrated by parents upon their children or vice versa; or—this being Kingland—by sundry ghoulies and ghosties and things that go bump in the night.

IT’s protagonists are the Losers—so named by their yahoo peers—a fetching group of 6 boys and one tomboy. Each is an outsider in some fashion, often denigrated: variously, the tomboy, a stutterer; Jew; brainy nerd; off-putting chatterbox. Each comes from a troubled social or family background. For instance, the tomboy is savagely mocked by mean girls for being dykish and a slut. (She’s not.) At home she’s tyrannized by a father seething with repressed incestuous desire.

For all their jibing, the Losers are touchingly supportive and winningly decent (King always treasures a kind heart). The members of such a group typically grow more whole psychologically as it evolves. The group identity forged is stronger than its parts. Before the film’s opening, one senses the youngsters have already begun drawing upon each other’s strengths, as they care for each other’s psychological bruises.

IT’s opening sequence skillfully encapsulates the terror to come. A winninglygmboy in a yellow slicker pursues his paper boat racing down the gutter in a drenching rain. It disappears into a sewer. A garishly painted clown head pops up behind the drain gate. Pennywise—so he calls himself—is merry, insouciant, and beneath his seductive affability, ineffably frightening.

He invites the boy, by name, to join his subterranean circus: “We all float down here” (a typical uncanny King catchphrase—how and why would you float in a sewer’s depths?). The youngster backs off, Pennywise gulls him into
reaching for his boat—and bites off his arm, killing him!

After the dead boy’s agonized brother (the stammerer) also sees the clown, each of the kids has a different, traumatic supernatural experience: a torrent of blood explodes from a bathroom sink; the elongated woman in a Modigliani-like portrait writthes into horrid life. During each manifestation, Pennywise is seen, heard, or his presence intimated by an eerily floating, blood-scarlet balloon.

Pennywise comprises King’s powerful reinvention of the “Evil Clown,” a signal example of the heimlich/unheimlich binary, uncannily conflating humor and horror. It’s been widely observed that a clown’s gaping grin and bumptious behavior are more likely to provoke angst rather than laughter in children. (Jungian researchers link the Evil Clown to the archetype of the benevolent/malevolent “Trickster” of many cultures.)

Delving in the library by the Losers’ quondam historian reveals that Derry’s unheimlich reality is, and has always comprised a scrim over Pennywise’s unheimlich inferno since the town was founded. Over several centuries, scores of children have disappeared or died in a succession of catastrophic fires, factory explosions, etcetera.

Derry turns out to be situated over a maze of ancient sewers, converging into a central pumping station. Once prized as a symbol of civic progress, it has decayed into the genre’s staple—the dark old house, where inchoate evil lies “below.” At some point the main sewer conduit became the entrance of Pennywise’s underground charnel house, in which his young victims “float.” (King perennially taps into the creepy horror of “what lies beneath”; Pennywise’s noxious domain evokes Gehenna; Hades; and sundry Christian, Islamic, and Buddhist infernal regions.)

The Losers eventually realize that Pennywise flourishes by feeding off their fears, and will only be conquered by descending into the sewer’s hellmouth and destroying him.

In Pennywise’s lazymrheine lair, they run a gauntlet of loathsome monsters and funhouse grotesqueries, until the tomboy’s slingshot turns magical, pierces Pennywise’s facade. The other Losers then attack him with whatever make-shift weapon at hand, until the earth swallows him up.

All this seems the stale stuff of hoary fairy tales. But a source of King’s success is his remarkable ability to newly mint fairy tales, myths, and sagas, notably those in which an omnipotent jabberwock-monster is defeated by a seemingly weak or inept child—or child-like—adversary.

Bettelheim was not the first to address the therapeutic value of these enduring narratives to children. King’s heroes, young or old, regularly undergo analogous quests, culminating in a newfound maturity, while satisfyingly scaring us out of our collective knickers.

Pennywise has only been vanquished for the present. As he sinks back into his cloacal sewer, he cackles that his clown persona is just another mask, concealing a being infinitely more malignant, that will return again. It testifies to their maturity that they recognize his threats conceal his fears—of them.

In the final scene, the Losers link arms in a charmed circle; swear a blood oath to return to Derry, no matter where they are, to confront Pennywise in his next cycle. Then, poignantly, each fades away.

IT isn’t a genre masterpiece like Frankenstein (1931), The Shining (1980), or Videodrome (1986). But the film is well directed (Andy Muschietti), scripted, and acted. The children’s performances are particularly fine.

Tim Curry’s Pennywise was greatly stroked, but Bill Skarsgard’s Evil Clown is much more nuanced, his voice shifting supply between merriment and menace. The CGI and other special effects are beyond awesome.

IT honors the unwritten contract between maker and viewer since the genre’s inception to scare us, but never to death. Such is not the case with a sub-genre of “cruel cinema” I’ve analyzed elsewhere, in which the horror picture so assaults viewers as to become a nightmare from which one doesn’t easily awaken so easily.

As a stoned buff of horror movies since adolescence—like King himself—I myself savor gorefest classics like Night of the Living Dead (1968). But I wouldn’t recommend such grisly fare to the faint of heart.

A note on the trashing of King’s work by literati like Harold Bloom. Bloom was said to be incensed when King was granted a lifetime achievement award from the National Book Awards association. A mere scribbler doesn’t get published in The New Yorker. I predict that if we manage to survive the very real horrors of our present world, a century from now, King—like Poe, Hawthorne, Philip K. Dick, and H. P. Lovecraft—will be treasured, long after Bloom and his censorious lot have been consigned to the dustbin of history.

**ADDENDUM**—The movie, like the novel, adroitly interpolates flash-forwards of the adult Losers, preparing to encounter Pennywise when he has emerged from his 27-year hibernation. In the next film, already in production, they confront the shapeshifting malignancy definitively. I won’t reveal the outcome, but one doesn’t have to be Nostradamus to predict a repeat of the current film’s staggering popularity and profitability.

**Reference**

The Truth About Shared Decision-Making

Dawn I. Velligan, PhD

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EDITOR'S NOTE—This summary is based on Dr. Velligan’s presentation at the 2017 Psychiatric Congress on Saturday, September 16, at 9 AM.

n the past several decades, clinical care has moved from a traditional provider-driven paternalistic model to one that values shared decision-making (SDM). SDM is a process in which both the provider and the patient are involved. The provider shares information about the alternatives, risks, and benefits of specific treatments and elicits input from the patient; the patient shares information about his or her preferences, values, and concerns and asks questions; and both parties work toward an agreement on the treatment to be implemented.

A focus on understanding preferences and values of the patient is particularly central to treatment outcomes in situations in which there is no clear “best” treatment and there are many choices with variable adverse-effect profiles. This is clearly the case in many areas of medical treatment including various cancers, diabetes, and psychiatric conditions.1-3 The Institute of Medicine calls for individuals’ values and preferences to guide all physical and mental health care.3

Empirical evidence indicates that involving patients in the treatment decision-making process leads to increased satisfaction with treatment, lower decision conflict arising from being better informed, better follow-through on treatment recommendations, and even improved outcomes for medical markers such as blood pressure and blood glucose.3,4

Despite its promise, it has been a slow process for SDM to be accepted in the mental health field relative to other areas of medicine. Provider-dominated decision-making characterizes many psychiatric consultations. This may reflect provider concerns about the effects of mental illness on patients’ ability to participate in SDM. Many individuals with serious mental illness suffer from cognitive impairments that may hinder their ability for complex cognitive processing. Moreover, some psychiatric conditions specifically affect judgment and decision-making. However, contradicting these apparent risks, many adults with serious mental illness frequently make competent and prudent treatment decisions.

To further complicate the picture, decision-making for doctors and patients is subject to multiple biases. Prescribers have biases based on habit (comfort or lack of comfort with a specific option) and perceived risk aversion. Patients as human beings are subject to appraisal biases including ignoring information that does not fit into preconceived ideas, giving more weight to negative information, and being affected by the context in which information is presented.1

Despite these pitfalls, patients routinely report wanting to be involved in decisions about their treatment. Many providers believe they are engaging in SDM, but 6 out of 10 patients don’t feel listened to during appointments.2 Doctors are often missing the profound impact on the patient of the power differential. The patient is in the doctor’s office, on the doctor’s schedule. He or she is told when to enter and leave. If the patient is more than 15 minutes late, the appointment is rescheduled. If the doctor is 15 minutes late, the patient is expected to wait. Staff have separate bathrooms. This context surrounding visits helps to create passivity and deference to the expert, even when the doctor believes SDM is taking place.4 Thus, it is necessary for the prescriber to engage in very specific behaviors to ensure that SDM is taking place.

According to Elwyn and colleagues,5 providers must engage in a number of steps to ensure that SDM is taking place, engages the patient, and offers hope. These include:

1. Choice talk, which involves making a statement that the 2 participants must think about what to do next, offering choices, emphasizing individual preferences

2. Option talk, which involves checking the patient’s knowledge, describing options in terms of harms and benefits, providing decision support, and summarizing using the teach-back method

3. Decision talk, which involves eliciting a preference and moving to a decision

Our research group has modified Elwyn’s model to include the responsibilities of the patient to Tell, Ask, Choose, and Review. Patient’s must Tell the doctor important information about their condition and context, Ask key questions about options, Choose or choose to defer choice, and Review the impact of their choice.

By training both providers and patients to engage in SDM using simple models that focus on specific behaviors, we may be able to increase the likelihood that SDM will take place in decision-making about treatment options in mental health.

References

Personalized Medicine in Psychiatry: The Tangible and Immeasurable Benefits of Measurement-Based Care

Whitney E. Black, MD

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Imagine treating patients with hypertension. Vital signs and laboratory tests from prior visits inform decisions to prescribe specific medications, dosing regimens, and other interventions. When patients come for follow-up, along with gathering subjective information and updating physical examination data, one obtains additional objective measurements. These data guide further decisions and are vital to tracking treatment responses.

How can psychiatrists provide consistent, high-quality care without using the full complement of available tools?

Measurement-based care

In psychiatry, measurement-based care has been defined as the systematic use of validated measures to monitor patient progress and directly inform care decisions. Evidence supports the effectiveness of measurement-based care in reducing time to treatment response, time to remission of symptoms, and treatment dropout. However, a recent Kennedy Forum issue brief indicates that fewer than 20% of psychiatrists consistently use measurement-based care in their treatment decisions. What are the barriers to adopting measurement-based care into routine psychiatric care? The literature has reported a range of issues, from the practical side of workflow integration, to philosophical disagreement, especially the belief that such practices interfere with the therapeutic relationship.

New technology, known as measurement feedback systems (MFS), can overcome many of the practical workflow barriers. Today’s MFS software can automatically assign patient-reported outcome measures (PROMs) based on diagnosis. These scores are collected and are available at the time of the visit, giving clinicians immediate access to actionable data. Many of these systems can be integrated directly into electronic health records, creating a seamless flow of data and documentation. Perhaps more than other specialties, given the tendency for some psychiatric practices to lack or utilize relatively fewer support staff, psychiatric providers may depend on these systems to track outcomes, while reducing administrative burden and enhancing quality of care.

Although many quality improvement initiatives elicit negative reactions from providers, the use of MFS may actually improve our capacity to connect with, understand, and support patients. The ability to monitor a patient between visits to detect changing symptoms or lack of response to treatment can provide valuable data in a timely way. By having immediate access to PROMs, the “vital signs” of our practice, before meeting with patients, better outcomes can be obtained in more efficient ways. With serially validated PROMs, we can minimize the time currently spent teasing out symptom criteria and reallocate this time to healing through human connection.

In this way, the use of such measures complements traditional methods of psychiatric practice, rather than being a mechanized and impersonal substitute for compassionate and caring human contact.

Successful incorporation of MFS-derived outcomes measures into routine practice will likely depend on adopting a new language for such measures. Terms such as “measurement-based care” conjure images of assembly lines and sterile transactions. The less tangible benefits, especially if derived from effective use of MFS, are completely misunderstood. When these measures are integrated directly into the electronic health record, the therapeutic alliance may actually be enhanced. I routinely share measurement results with my patients and reflect on how the data correlate with their subjective experiences. This has increased patients’ engagement in their care and has ensured a better understanding of their experiences.

The FDA defines “personalized medicine” as collecting objective information about patients to tailor treatment more specifically to their individual characteristics, needs, and preferences. I prefer the term “relationship-based care” for this form of personalized medicine in psychiatry.

Conclusion

It is time for psychiatry to adopt the treat-to-target model that has led to significant reductions in morbidity and mortality in other medical specialties. Measurement-based care will help accomplish that goal. However, while I encourage psychiatry to focus on objective data, we must recognize the less tangible benefits of this practice. A practical, data-driven approach can contribute to significant additional benefits by maximizing the time we devote to meaningful relationships with our patients—the value of which may be immeasurable.

Dr. Black reports no conflicts of interest concerning the subject matter of this article.

References


How can psychiatrists provide consistent, high-quality care without using the full complement of available tools?
Treatment-Resistant Bulimia Nervosa

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which has fairly widespread use in BN despite well-known tolerability issues and the potential adverse effect of unhealthy weight loss in BN patients striving for thinness. It may surprise some clinicians to know that this approach is based on randomization to topiramate or placebo of only approximately 130 patients, for a period of just 10 weeks. Despite the apparent limited benefit of medications in BN, there has been virtually no research in this area for more than a decade.

Potential mechanisms of nonresponse

Improved understanding of the neurobiology and associated features of BN may provide both an explanation for poor response to evidence-based treatment, and a framework for improved treatment approaches. Impaired inhibitory control and aberrant reward responsivity and reward-based learning may contribute to the affective dysregulation, binge eating, purging, and other impulsive behaviors often reported by individuals with BN. Extant neuroimaging findings in BN suggest abnormal functioning of the corticostriatal and corticocircuits that support these processes, and this altered functioning has been linked to increased bulimic symptom frequency. Dysfunction in these circuits may leave patients with powerful urges to inappropriate or excessive eating or to purge, and, in combination with impaired learning, may interfere with response to treatment.

Strategies for treatment-resistant BN

Designing successful interventions requires consideration that abnormal neurobiological functioning may contribute to BN and associated behaviors, and that these behaviors appear to serve the purpose of temporarily reducing intolerable emotional intensity. Specifically, treatments for refractory BN may include a focus on skills and strategies designed to help patients regulate emotions and cope with altered inhibitory control and reward sensitivity.

Developments in psychotherapeutic strategies. Psychotherapeutic interventions for treatment-resistant BN may specifically focus on skills that help patients cope with their dysregulated emotions, thereby reducing impulsive behaviors. Recent treatments developed to address emotion dysregulation within BN include integrative cognitive-affective therapy, adaptations of CBT, and dialectical behavior therapy (DBT).

DBT originally was developed for patients with intense emotion dysregulation, borderline personality disorder, and/or suicidality, and has been adapted and studied for use with eating disorders. With its heavy emphasis on skill development for tolerating distress and regulating emotions, along with its structured approach to treating complex comorbidities, DBT may be particularly effective in mitigating biologically driven vulnerabilities to unstable affect and maladaptive, impulsive behaviors.

Emerging pharmacological strategies. Considering the prevalence and morbidity of BN, along with the limited efficacy of antidepressants and safety concerns about topiramate for many patients, the lack of new research into pharmacological treatments during the past decade and present day is notable. Recently, a few encouraging but very small open series and case reports have been published. Some of these have utilized antiepileptic drugs—namely, zonisamide and lamotrigine, which warrant further exploration for treatment-refractory BN. Similar to topiramate, zonisamide has an adverse-effect profile that may limit its use in patients with eating disorders. Lamotrigine, with its relative weight neutrality, greater tolerability, and demonstrated benefit in other conditions characterized by affective dysregulation and impulsivity (eg, bipolar disorder), may hold the most promise. The decreases in emotional and behavioral dysregulation associated with lamotrigine may blunt or delay impulsive urges enough to allow patients to use skills, ultimately permitting engagement with empirically supported psychological treatments. However, controlled trials of lamotrigine are needed.

Recent FDA approval of lisdexamfetamine (a CNS stimulant) for binge eating disorder has heightened interest in potential use of such medications in BN. Some investigators hypothesize that CNS stimulants may address inhibitory control deficits or deficient reward systems in dysregulated eating disorders in a similar manner as in ADHD. A retrospective series published earlier this year showed large reductions in binge and purge symptoms in 6 patients with chronic BN. While this is intriguing, substantial risks associated with use of these controlled substances in dysregulated BN may make CNS stimulants prohibitive.

The relatively weight-neutral atypical antipsychotic aripiprazole showed benefit as augmentation to antidepressants in 2 small groups of treatment-refractory BN case reports. It is interesting to speculate whether the partial-agonist properties of aripiprazole may improve stabilization of dopamine-serotonin neurotransmitter systems, which have shown abnormalities in BN.

Treatment of comorbidities. Although previous existence among practitioners that co-occurring disorders must be addressed in BN treatment, when and how to do so remains a subject of much debate and is a critical consideration in treatment planning. Medication management of comorbidities such as MDD, bipolar disorder, and anxiety disorders is beyond the scope of this article, but is an important aspect of comprehensive care that may improve the capacity of BN patients to engage in treatment. Evidence-based protocols (eg, CBT for depression, prolonged exposure for PTSD) exist for most comorbidities, but it can be difficult to know how to integrate those treatment protocols with the treatment of the primary eating disorder.

Treatment can take place sequentially, or it can follow an integrated approach that treats all conditions concurrently. Sequential treatment may be advantageous in that it allows the clinician to address safety concerns presented by the eating disorder first, may reduce barriers to the effectiveness of the other treatment, and may be logistically more practical. However, treating one cluster of symptoms may result in worsening of other behaviors, and this cycling may prevent recovery from both disorders. Thus, more recently, concurrent or integrated treatments across comorbidities have become the preferred approach. Regardless of the chosen timing, comorbid conditions should be addressed with evidence-based treatment.

For Melia, the combination of DBT and lamotrigine was very effective. Melia had begun to learn DBT skills in past treatment episodes, but reported difficulty applying the skills because her impulsivity was so strong that she felt there was “no time” between an urge and a behavior to attempt to use the skills. With the addition of lamotrigine, she still experienced urges to binge, purge, shoplift, and self-harm, but she demonstrated increased ability to delay urges long enough to call her therapist for skills coaching. DBT hierarchical helped her therapist organize and prioritize Melia’s treatment targets.

DBT has a focus on helping the patient build a “life worth living” outside the disorder. For Melia, this was difficult because she felt that anything short of immediately completing school with top grades and going to law school would be failure. During treatment, she was able to be less judgmental of herself, and she got a temporary job as a paralegal while she focused on recovery. Her depression and anxiety also improved, and she gained more insight into balancing career and other life goals. Ultimately, she graduated college with plans to attend law school.

Conclusion

Despite significant progress in our understanding of the biological substrates of BN during the past decade, traditional evidence-based treatments fail to help many patients achieve full remission of symptoms. Development and rigorous evaluation of new treatment approaches—particularly those that target characteristics of comorbid disorders—remain crucial tasks in decreasing suffering for patients such as Melia.

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TREATMENT RESISTANCE

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Most of the literature on treatment-resistant bipolar disorder is related to treatment of acute episodes of mania or depression. There is no formal universal definition of treatment resistance; proposed criteria have included a specific number of failed medication trials; incomplete or unsatisfactory response to treatment (usually determined by symptom rating scales); unsuccessful response for a specified duration of treatment; failure to respond to a phase of bipolar disorder, poor response to all medication and nonmedicinal interventions, or lack of response to only “evidence-based” (usually FDA-approved) medications for bipolar disorder.

It should be noted that the FDA has approved both vagus nerve stimulation (VNS) and transcranial magnetic stimulation (TMS) for treatment-resistant depression: VNS, if the patient has failed 4 or more different medication trials; and TMS after only 1 adequate medication trial. We consider a patient with bipolar disorder treatment resistant if trials of all medications approved by the FDA for bipolar disorder have failed. This article focuses on treatment resistance to medications in adult male and non-pregnant adult female outpatients with any type of DSM-5 diagnosed bipolar disorder.

Possible contributing factors to treatment resistance

Although the severity of the bipolar disorder and the degree of response to medical treatments are usually considered predominantly under genetic or other endogenous influences, several non-biological factors often

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Contribute significantly to treatment resistance (Table 1). Some of these factors can be successfully addressed, often resulting in a better prognosis. For clinical purposes, it is more useful to conceptualize bipolar disorder as a spectrum condition rather than a true “bipolar” disorder, since this approach may lead to more accurate recognition of the active symptoms of the current episode. Such recognition is crucial because these findings, rather than the diagnostic subtype of the bipolar disorder as defined by DSM-5, should determine the choice of medications, especially because the diagnosis of MDD has been redefined in DSM-5 to include some hypomanic/manic symptoms.

Some clinicians find symptom checklists or scales helpful in supplementing findings on the mental status examination. Symptom recognition is especially important when medicating patients who have bipolar disorder with mixed symptoms because failure to recognize less obvious or “soft” hypomanic symptoms (insomnia, anxiety, irritability, rapid thoughts, and rumination) can lead to prescribing antidepressants, which will offer no therapeutic benefit and may even worsen activation symptoms. (The reader is referred to 3 helpful and thoughtful references for a more thorough discussion of this important clinical issue.)

Before medications are initiated, several potential obstacles to successful treatment of bipolar disorder should be addressed, especially for outpatients. Significant others of the patient should be included in the initial evaluation and during the course of treatment if necessary, especially if the patient is unable to recognize or communicate symptomatology well.

Patients who use even small or moderate amounts of alcohol or recreational drugs (including marijuana) should be informed that any continued use can interfere with the therapeutic effects of prescribed bipolar medications. Concurrent use of some psychiatric (antidepressants) and non-psychiatric (eg, steroids, opioids) mood-destabilizing medications should be discontinued to determine whether they are opposing the therapeutic effects of antimanic agents.

Volitional unhealthy lifestyle behaviors can also have an adverse effect on the prognosis of bipolar disorder. Patients should be informed that controllable poor sleep habits (staying up late on the internet), predictable and avoidable stressful situations, and irregular medication compliance can neutralize or outweigh the positive effects of prescribed medications. Moreover, frequent exercise and the stability of regular routines, such as healthy eating habits and good sleep hygiene, can enhance treatment outcomes.

**Chronic insomnia and chronic anxiety**

A significant number of patients with bipolar disorder, especially those with mixed symptoms, experience chronic insomnia and chronic daytime anxiety, often for years without interruption. These symptoms are not true mood symptoms and may be related to an overactivated generalized hyperarousal state that might be caused by a systemic dysfunction of the hypothalamic-pituitary-adrenal axis. Aggressive medication treatment of these 2 persistent symptoms is indicated because both are associated with a diminished prognosis, and both can cause impaired daytime functioning and distress. In addition, chronic insomnia in bipolar disorder is associated with impaired cognition, worsening of hypomanic/manic symptoms, and increased risk of suicide.

In most cases, the benefits of maintenance treatment, even with benzodiazepines, usually outweigh the risks if the patient does not have a history of substance abuse and is monitored closely. Most large-scale surveys of different classes of medications taken by patients with bipolar disorder reveal that benzodiazepines are prescribed for a substantial number of patients, probably because their chronic insomnia and anxiety symptoms are not adequately controlled by maintenance mood-stabilizing medications alone.

**Psychotherapy**

Although medications are the mainstay of treatment of bipolar disorder, some patients benefit from adjunct psychosocial interventions, which can be provided by the treating psychiatrist or by a non-MD counselor working in parallel with the prescribing physician. According to some studies, the following psychotherapeutic modalities with pharmacotherapy can be helpful in reducing the risk of relapse, improving treatment compliance, and decreasing the number and duration of hospitalizations: psychoeducation, cognitive behavioral therapy, interpersonal and social rhythm therapy, family counseling, and functional rehabilitation training. Referrals for this specialized treatment should be made to mental health professionals who have experience and expertise in working with bipolar disorder.

**The art of psychopharmacology**

The psychiatrist who provides pharmacological treatment for patients with bipolar disorder can improve the prognosis for treatment-resistant bipolar disorder by skillful and strategic management of medications. Helpful general prescribing principles are listed in Table 2. A significant number of psychiatric outpatients are sensitive to and respond to lower than standard doses of CNS medications. For this reason, starting doses for any psychiatric medication prescribed for the first time to outpatients should be very conservative, and increases in doses should be small and gradual. A good example is lithium, which can be effective and better tolerated in outpatient monotherapy or as an adjunct agent at doses that produce a blood lithium level of 0.5 mmol/L, or lower. We have had success utilizing a compounding pharmacy to produce medications for sensitive patients at strengths lower than the manufacturer’s recommended minimum doses.

Most patients with bipolar disorder require polypharmacy. In these cases, the prescribing physician should not change more than one medication at a time because the cause of any positive or negative effects will be unclear if more than one medicine is changed simultaneously. The cost and accessibility of a bipolar disorder medication should be considered and discussed with the patient before it is initiated because some expensive brand products may not be covered by the patient’s health insurance, or the high copay may be unaffordable. Providing samples to initiate treatment can be helpful in these situations.

Patients who have bipolar disorder should be alerted to the risk of a switch to hypomania/mania when antidepressants are initiated, even when they are being added to an antimanic medication. Furthermore, it is important for the treating psychiatrist

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**TABLE 1. Possible contributing factors to treatment-resistant bipolar disorder**

- Inability to identify “soft” hypomanic symptoms
- Incorrect diagnosis of bipolar disorder
- Incorrect recognition of bipolar disorder phase
- Patient is poor historian (failure to use collateral sources and prior treatment records)
- Poor patient compliance
- Concurrent alcohol or substance use
- Concurrent use of destabilizing medication (psychiatric and nonpsychiatric)
- Concurrent acute or chronic medical illness
- Inadequate medication supervision by treatment provider
- Inadequate medication trial
- Limiting treatment choices to “evidence-based” medications only
- High starting dose or rapid dose increase of medications
- Failure to recognize bipolar disorder is usually a chronic and recurrent illness

**TABLE 2. General medication guideline suggestions**

- Do not change more than one medication at a time
- Choose medications for specific target symptoms
- Prioritize treatment of severe, uncomfortable, or disabling symptoms (insomnia, anxiety, panic attacks, psychosis)
- Use benzodiazepines as adjunctive treatment for symptoms of bipolar disorder that do not respond to maintenance mood medications (insomnia, anxiety, panic attacks)
- Consider cost and accessibility of medications
- Educate patient about medication before initiation of treatment (provide literature)
- Provide proactive supervision of medication changes when patient is unstable (frequent phone calls or office visits)
- Be aware that formal treatment guidelines can be helpful, but must have imperfections
- Document rationale for non-FDA-approved medications if not considered standard of care
- Start medications at low doses and increase dose cautiously, especially in elderly patients
- Become familiar with different forms and strengths of bipolar disorder medications (brand vs generic, capsules vs tablets, liquid, compounded, etc)
to be aware of the risk-to-benefit ratio when introducing antidepressants in different treatment situations. Helpful consensus recommendations for the use of antidepressants in bipolar disorder have been provided by a task force convened by the International Society for Bipolar Disorders and are listed in Table 3.13

Consensus treatment guidelines

During the past several years, multiple formal consensus guidelines for medical treatment of bipolar disorder have been published, usually by a group of academicians and experts on psychiatric organization committees from different countries. Most of these guidelines are organized into different tiers of preferred treatments that are ranked according to evidence-based supporting published research data and the strength of methodology utilized in each study. More recent guidelines include neuromodulation interventions such as TMS, VNS, and deep brain stimulation, although none of these modalities are FDA approved for bipolar disorder. These newer brain stimulation treatments for depressive episodes of bipolar disorder show encouraging, but limited, results.11 Nonetheless, we have treated a few medication-refractory depressed bipolar patients successfully with both VNS and TMS.

Most psychiatrists who treat bipolar disorder are aware that many patients do not respond to FDA-approved medications for bipolar disorder and that trials of off-label, less-often prescribed agents are acceptable and preferable to no further treatment, especially for patients who refuse ECT or in whom ECT has failed. (The reader is referred to 2 publications as helpful references that include both FDA-approved and off-label options for treatment-resistant bipolar disorder.12,13) Our proposed guidelines for treatment options are listed in order of preference for the 3 main phases of bipolar disorder in Table 4.

<table>
<thead>
<tr>
<th>TABLE 3. Summary of Consensus Recommendations for Antidepressant Use in Bipolar Disorders by International Society for Bipolar Disorders Task Force</th>
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<tbody>
<tr>
<td>Adjuvant AD for major depressive episode</td>
</tr>
<tr>
<td>Adjuvant AD for maintenance treatment</td>
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<tr>
<td>AD monotherapy for major depressive episodes</td>
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<tr>
<td>AD associated with switch to mania/hypomania, mixed symptoms, or rapid cycling</td>
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<tr>
<td>AD use in mixed states</td>
</tr>
<tr>
<td>AD with increased risk of switch (TCA and SNRI)</td>
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<td>AD, antidepressant.</td>
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</table>

In many instances, patients with treatment-refractory symptoms are satisfied with a partial benefit from a medical treatment, while they are waiting for the next new treatment for bipolar disorder to become available, if the response is noticeably better than no treatment, especially for the most uncomfortable and disabling symptoms. Lastly, the literature supports the use of 2 more treatments, ECT and clozapine, when all other options have failed.14

The authors report no conflicts of interest concerning the subject matter of this article.

References

<table>
<thead>
<tr>
<th>TABLE 4. Proposed guidelines for treatment options (in order of preference) for the 3 main phases of bipolar disorder</th>
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</thead>
<tbody>
<tr>
<td>Acute hypomanic/manic and mixed episodes</td>
</tr>
<tr>
<td>• Monotherapy or adjunctive other FDA-approved medications: carbamazepine, chlorpromazine</td>
</tr>
<tr>
<td>• Monotherapy or adjunctive other FGA</td>
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<tr>
<td>• Other anticonvulsants (adjunctive): oxcarbazepine, pregabalin, gabapentin, levetiracetam</td>
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<tr>
<td>• Benzodiazepines (adjunctive)</td>
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<tr>
<td>• Other medication families (monotherapy or adjunctive): calcium channel blockers, memantine</td>
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<tr>
<td>• Clozapine</td>
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<tr>
<td>• ECT</td>
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<tr>
<td>Major depressive episodes</td>
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<tr>
<td>• Quetiapine (FDA approved)</td>
</tr>
<tr>
<td>• Lithium (monotherapy or adjunctive)</td>
</tr>
<tr>
<td>• Asenapine</td>
</tr>
<tr>
<td>• Aripiprazole (monotherapy or adjunctive)</td>
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<tr>
<td>• Anticonvulsants (monotherapy or adjunctive): oxcarbazepine, levetiracetam, carbamazepine</td>
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<tr>
<td>• Antidepressants (monotherapy or adjunctive)</td>
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<tr>
<td>• Other medications (monotherapy or adjunctive): modafinil or armadafinil, pramipexole, stimulants (methylphenidate), thyroid (T3)</td>
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<tr>
<td>• Light therapy</td>
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<tr>
<td>• Transcranial magnetic stimulation</td>
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<td>• ECT</td>
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<tr>
<td>• Vagus nerve stimulation</td>
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<tr>
<td>• Adjunctive ketamine</td>
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<tr>
<td>Continuation/maintenance/preventive treatment</td>
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<tr>
<td>• Lithium (FDA approved)</td>
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<td>• Lamotrigine (FDA approved)</td>
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<tr>
<td>• FDA-approved SGA (monotherapy or adjunctive)</td>
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<tr>
<td>• Non-FDA-approved SGA (monotherapy or adjunctive)</td>
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<td>• Carbamazepine (monotherapy or adjunctive)</td>
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<td>• Transcranial magnetic stimulation</td>
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<td>• Clozapine (monotherapy or adjunctive)</td>
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<td>• ECT</td>
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FJA, first-generation antipsychotic; SGA, second-generation antipsychotic.

In this 2-part series, the origins of antidepressants in the early 1900s and the discoveries that led to FDA approval of the first antidepressant in 1958 were reviewed in Part 1 (Psychiatric Times, October 2017, page 23). The development of the monoamine hypothesis of depression, our current FDA-approved armamentarium, and antidepressant augmentation strategies as well as the first FDA approval of an augmenting agent in 2007 were discussed.

Part 2 explores the significant pharmacokinetic and pharmacodynamic heterogeneity of current antidepressants and provides a review of the many potential drug targets that exist—with a focus on the serotonin system as we now understand it. Part 2 concludes with an overview of antidepressant drug development that is currently underway to hopefully provide novel agents.

Pharmacokinetics and pharmacodynamics: variety is the spice of life

No single antidepressant is considered superior. As such, choosing which antidepressant to prescribe to a patient is the result of a thoughtful analysis that includes many factors, both pharmacokinetic and pharmacodynamic. The analysis follows a careful history (Table 1). In addition, the patient’s understanding of depression as a psychiatric disorder that may improve with antidepressant treatment, his or her opinion about the use of antidepressant medication, ability to comply with a structured medication regimen, and competent understanding of the risk-to-benefit ratio of antidepressant treatment must be considered.

The criteria for a major depressive episode include both insomnia and hypersomnia, psychomotor retardation and agitation, decreased and increased appetite, and weight gain and loss. Hence, the specific symptoms of the patient’s depressive episode can inform which antidepressant choice may best improve these symptoms and which may worsen them. A comorbid psychiatric diagnosis can inform the choice of an antidepressant, which may help symptoms of both diagnoses. Family history can provide many clues about the likelihood of medication response, as shared genetic factors can contribute to the response to a particular antidepressant.

It is vital to obtain an accurate list of all current prescription medications, along with the reason it is being prescribed, its dose, and the duration of treatment. Factoring in the potential for drug-drug interactions on the basis of pharmacokinetics and pharmacodynamics can prevent significant adverse effects and possibly life-threatening outcomes.

Herbal supplements that patients often forget to list can have a major effect on a drug. One example is St John’s wort, which is a serotonin reuptake inhibitor and also a potent inducer of cytochrome P450 (CYP450) 3A4—the
most common metabolic pathway of all prescription drugs. St John’s wort can dramatically lower the serum level of a medication that is metabolized by CYP450 3A4, which renders it less effective and possibly ineffective. Moreover, the use of an antidepressant that also has activity as a serotonin reuptake inhibitor can increase the risk of serotonin syndrome.

Many recreational drugs can contribute to antidepressant failure. Not uncommonly, use of the recreational drug may significantly contribute to the patient’s presenting symptoms. Alcohol use disorder can result in significant depression and anxiety. Excess caffeine intake can contribute to insomnia and psychomotor hyperactivity. Cigarette smoking (the smoke, not nicotine itself) results in significant induction of CYP450 1A2 levels, which will hypermetabolize any drug that utilizes this pathway. Methadone can cause depression and weight gain. Cocaine withdrawal can mimic a major depressive episode. These are just a few common examples.

If a patient has a history of nonadherence or poor adherence to treatment, consideration should be given to the use of a drug with a long half-life. Alternatively, recruiting a partner, friend, or family member to monitor medication adherence can have a huge impact on treatment effectiveness. Assessing the patient’s capacity to manage the medication regimen is also important. A person with psychomotor retardation, poor motivation, or cognitive impairment is less likely to successfully comply with treatment. Finally, a patient’s access to a particular treatment needs to be considered. Lack of health insurance, lack of medication coverage, rigid formularies, and geographical isolation can create barriers to access of medications. Tables 2 and 3 list pharmacokinetic and pharmacodynamic issues that need to be considered when choosing an antidepressant.

The more we learn, the less we know

In the early days of antidepressants, the 3 monoamines that helped transform our understanding of depression—serotonin, dopamine, and norepinephrine—created the hypothesis that changes in the brain levels of these neurotransmitters could treat depression. The importance of these 3 monoamines gained greater momentum in our understanding of mental illness as our medication armamentarium grew.

With the antipsychotic efficacy of chlorpromazine, it was discovered that too much dopamine in one part of the brain (mesolimbic tract) seemed to be related to psychosis and mania. Too much norepinephrine in another part of the brain ramped up anxiety and panic. Too little dopamine in the prefrontal cortex resulted in cognitive dysfunction and inattention. Decades of research in the basic science laboratories of universities around the world began to unravel the complexity of the monoamine story, which went far beyond a monoamine and its associated receptor communicating in a synapse of a neuron in the brain.

The completion of the human genome project in 2003 allowed for the identification of the many subreceptors, gene promoter variants, and single nucleotide polymorphisms that all contributed to individual variations to drugs. More recently, the field of epigenetics has exploded, which adds yet another complex layer to gene expression. Significantly, an individual’s experiences throughout life have been shown to affect and change these epigenetic factors.

To appreciate just how far we have come since the FDA approval of iproniazid in 1958, let us explore the peeling of just the serotonin onion (Table 4). Three scientists who were studying hypertension at the Cleveland Clinic in 1948 discovered a molecule released from platelets that resulted in vasoconstriction, synergistically working with the platelets to stop bleeding. They named this new vasoconstrictor serotonin. Subsequently, it was established that 90% of serotonin is in the gastrointestinal tract, and the remaining 10% is in the brain and in platelets.

The next challenge was to discover serotonin’s role in the 3 organ systems. A serotonin receptor was discovered, which created a logical sequence of serotonin's involvement in neurotransmission.

Table 1 – Suggested variables to be included in an analysis before making a treatment decision

- The specific symptoms of the primary diagnosis that is about to be treated
- Past medication trials (including dose, duration, and outcome)
- Past medical and psychiatric diagnoses, family history
- Currently prescribed medications from all other providers
- Current use of supplements and herbs
- Current recreational substance use
- Likelihood of compliance
- The patient’s ability to manage the proposed medication regimen
- Recent laboratory results
- Neuroimaging reports
- Patient’s access to treatments

Table 2 – Important pharmacokinetic properties to consider about any medications that we are about to prescribe

- The drug’s half-life
- Time to maximum concentration after a dose is taken (T_{max})
- Maximum concentration after each dose (C_{max})
- Percent of protein binding (a proxy for fat solubility)
- Preferred route of administration
- Should the drug be taken with food, without food, 1 hour before/after a meal?
- Is the drug affected by P-glycoproteins (especially in the gut or at the blood-brain barrier)?
- Is the drug metabolized by any cytochrome P450 (CYP450) isoenzymes?
- Is the patient taking any medications or substances that can affect the functioning of any of the phase II conjugation enzymes (inducers or inhibitors)?
- Is the drug metabolized by phase 2 conjugation (glucuronidation, sulfation, and methylation)?
- Is the patient taking any medications or substances that can affect the functioning of any of the phase II conjugation enzymes (inducers or inhibitors)?
- Has the patient had pharmacogenomic testing?
- Did the pharmacogenomic testing provide actionable information about the CYP450 enzymes or glucuronidation enzymes that are involved in the drug’s metabolism (poor, intermediate, extensive, or ultra-rapid metabolizer)?
- Is the patient’s cardiac output outside the normal range?
- Does the patient have any hepatic or renal disease?
- Is the drug a pro-drug, an active drug, a pro-drug and active drug?
- How does the pro-drug convert to its active form, and what can reduce or increase that conversion rate?

Table 3 – Important pharmacodynamic properties to consider about any medication that we are about to prescribe

- Does the drug bind to any neurotransmitter synaptic reuptake pump in a manner that will change the activity of this pump in any way?
- Does the drug affect any significant enzymes involved in the synthesis or degradation of a neurotransmitter?
- Does the drug function at a neurotransmitter receptor as an agonist, partial agonist, antagonist, or inverse agonist?
- What are all the pharmacodynamically relevant binding affinities of the drug that may have clinical relevance (receptors, enzymes, transport pumps, other)?
- Are there any pharmacodynamic synergistic or antagonistic effects between the drug and any other drug, endogenous neurotransmitter, food substance, herbal supplement, or recreational drug that the patient takes or might take?

Continued from page 37

tessor), it results in many possible intracellular processes that can ultimately affect induction or suppression of gene expression, or activation or suppression of numerous intracellular processes.

The first serotonin receptor discovered was named the 5HT-1 receptor. Further research found a distinct second serotonin receptor, named 5HT-1B, while the first serotonin receptor was renamed 5HT-1A. In addition, a third serotonin receptor was identified: 5HT-1C. Careful analysis of these receptors’ amino acid sequences, and the discovery of additional serotonin receptors, indicated that there were different “families” of receptors that bound serotonin. Consequently, because of differences in their amino acid sequences, these serotonin receptors could be subdivided by similarities and differences.

The 5HT-1C receptor was structurally more similar to the 5HT-2A and 5HT-2B receptors than the other 5HT-1 receptors, so it was renamed 5HT-2C. To this day, there is no 5HT-1C receptor, but we now have 5HT-1D, 5HT-1E, and 5HT-1F receptors.

In 1993 the seventh and final family of serotonin receptors was discovered, appropriately named the 5HT-7 receptor. With the completion of the human genome sequencing in 2003, it is well accepted that there are no additional families of serotonin receptors. Having so many variations for the activation of any given G-protein at the cell surface allows for infinite possibilities of postsynaptic neuronal response to a single neurotransmitter, such as serotonin.

However, it would be too easy if the story ended here. Each gene that codes for the mRNA of each receptor contains introns and exons, which allows each serotonin subreceptor to be spliced in alternative sequences, providing another layer of complexity.

A single gene for a single receptor can have a range of single nucleotide polymorphisms (SNPs) that preserve the function of the gene but result in a range of binding affinity variability or response variability for the same neurotransmitter—in this case, serotonin. The change in a single nucleotide of one gene can occur in many different locations, each of which can alter the gene’s function in different ways. The SNPs can occur on the promoter region of the gene’s promoter sequence (greater, normal, or lesser gene production); nucleotide polymorphisms of the structural gene product (site of serotonin occupancy, allosteric site affecting site of occupancy); polymorphisms of the gene’s promoter sequence (greater, normal, or lesser gene production).

Epigenetic modifications of the genome
- Methylation of promoter sequence preceding structural gene
- Acetylation of associated histones affects gene access

Table 4 – The various elements of the serotonin system

- Synthesis of serotonin (many enzymes and other molecules involved)
- Transport of serotonin into presynaptic vesicles in the neuron
- Release of serotonin from storage vesicles into the synapse
- Reuptake of serotonin into the presynaptic neuron (serotonin reuptake pumps)
- Activity at serotonin receptors: pre- and post-synaptic
  - Seven families of serotonin receptors: most families with sub-families
  - Receptor type: ionotropic (5HT-5) or metabotropic (G-protein coupled; 5HT-1, 5HT-2, 5HT-4, 5HT-5, 5HT-6, and 5HT-7)
  - Receptor function: inhibitory (5HT-1 and 5HT-5) or excitatory (5HT-2, 5HT-3, 5HT-4, 5HT-6, and 5HT-7)
- Genetic variations resulting in heterogeneity of all gene products
  - Messenger RNA from each gene product, with introns and exons: gene products include receptors, enzymes, transport pumps; variable splicing creates heterogeneity of final gene product
  - Pharmacogenomic variability of the serotonin system gene product: single nucleotide polymorphisms of the structural gene product (site of serotonin occupancy, allosteric site affecting site of occupancy); polymorphisms of the gene’s promoter sequence (greater, normal, or lesser gene production)
- Breakdown of serotonin by monoamine oxidase and other enzymes

Alternatively, SNPs can occur at some structural site in the gene, which can directly affect the 3-dimensional structure of the neurotransmitter-receptor interface, or have a distant allosteric effect on the receptor that also influences receptor function. In both cases, the SNP on the structural region of the receptor’s gene can result in 3 different outcomes: no change in receptor activity, a decrease in receptor activity, or an increase in receptor activity.

**Figure.** A simplistic rendering of several of the different sites that antidepressant drugs and nutraceuticals can target to affect the serotonergic monoamine system.
One of the many studies that resulted from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial supports this idea of heterogeneity. McMahon and colleagues1 report, “Participants who were homozygous for the A allele had an 18% reduction in absolute risk of having no response to treatment, compared with those homozygous for the other allele.”

A comprehensive review summarized much of the science related to the impact of epigenetic changes on depression, and how these epigenetic modifications appear to be reversed with current antidepressant treatments. This ongoing research provides a glimpse into the evolving understanding of the relationship between epigenetics and depression.2 Epigenetic modifications that affect levels of brain-derived neurotrophic factor (BDNF) and the glucocorticoid receptor have been most studied. When the brains of individuals who had a history of childhood abuse and committed suicide were examined, variations in the degree of methylation of the promoter sequence of the glucocorticoid receptor were discovered. Several studies demonstrated a decrease in DNA methylation (which would increase gene transcription) associated with an increase in BDNF in individuals treated with various antidepressants.3

An important paradigm shift occurred when drug development moved from a focus on blocking serotonin reuptake pumps to targeting specific serotonin receptors. Arguably, blocking a serotonin reuptake pump is a very crude way to modulate the serotonin system. The result is a global increase in synaptic serotonin, which results in the agonism of all 7 serotonin receptor families and their associated subreceptors.

Post-synaptic serotonin receptors can execute their message on many different neuronal types. Post-synaptic serotonin receptor modulation may ultimately result in changes in concentration of a different neurotransmitter in a different part of the brain. Downstream effects of serotonin receptor activity may increase or decrease synaptic levels of serotonin, dopamine, norepinephrine, acetylcholine, glutamate, and GABA. In addition, serotonin receptors can regulate prolactin, oxytocin, cortisol, and substance P, just to name a few.

When you extrapolate the complexity of the serotonin system to all neurotransmitters that may affect depression, an infinite possibility of drug targets exist. This is very good news for the future of drug development to treat depression—thus far, we have only scraped the surface of potential mechanisms of action.

Looking to the future: opioids, magic mushrooms, and Special K

Research on novel antidepressant molecules that function outside of the monoamine hypothesis of depression has been somewhat of a roller coaster over the past 3 decades. Initially promising drug classes such as neuropeptide Y modulators, substance P analogs, corticotropin-releasing hormone (AKA factor) receptor antagonists, and metabotropic glutamate receptor agonists (especially subtypes 2 and 3) ultimately failed as treatment options. One continued frustration and clinical limitation of our current antidepressants that follow the monoamine mechanism is that it can take from 2 to 8 weeks to achieve an adequate antidepressant effect. It appears that a common denominator of the delayed antidepressant response correlates with increasing levels of BDNF as the depression lifts. This increase in BDNF is associated with increased synaptogenesis in the brain’s hippocampus—a crucial gateway connecting memories and emotions—which may often be atrophied in cases of chronic depression and chronic stress. When the depression has resolved, the hippocampus increases in size.

The recent excitement about ketamine is that it has been shown to have immediate antidepressant effects, which correlate with increasing brain levels of BDNF.4 Ketamine is a racemic mixture of S-ketamine (esketamine) and R-ketamine (arketamine), and both molecules are antagonists at the glutamate NMDA ion channel. Esketamine is 3 to 4 times more potent than arketamine. Arketamine appears to have a greater antidepressant effect than esketamine. Ketamine continues to be aggressively studied as a possible “next-generation” antidepressant, and the racemate esketamine delivered intranasally is likely to be the first formulation to apply for FDA approval.

Both esketamine and arketamine are metabolized to hydroxynorketamine, which activates the glutamate AMPA ion channel. Increasing AMPA glutamate ionotropic receptors may produce an antidepressant effect, and with no dissociative adverse effects and no abuse potential. This metabolite has no activity on the NMDA glutamate ion channel and may be responsible for the increase in BDNF.4 The discovery in 2016 that hydroxynorketamine has antidepressant efficacy in mice (likely related to increased BDNF), without the abuse potential or dissociative adverse effects of ketamine, may provide a new avenue for drug development.

The clinical use of ketamine for the treatment of refractory depression is still considered experimental, and much remains to be learned about optimal dosing, delivery mechanisms, short- and long-term adverse effects, and duration and frequency of treatment.

Another class of drugs with a resurgence of interest for the treatment of refractory depression is the hallucinogens. Psilocybin, LSD, and mescaline are all serotonin analogs that have significant agonism at the 5HT-2A receptor. Most of the recent studies in refractory depression have involved psilocybin.

In one study, patients with treatment-resistant depression received 2 oral doses of psilocybin (10 mg and 25 mg in a supportive setting, 7 days apart). One week after they received the second dose, 67% of patients had an improvement in symptoms, and 58% maintained this response at 3 months.5 Although the data on psilocybin are in the early stages, and the current studies are open label, the findings are very intriguing.

There has been increased interest in the role of inflammation in causing depression, exacerbating depression, and/or contributing to non-response in patients with treatment-resistant depression.

The buprenorphine-samidorphan combination results in kappa-opioid antagonism. Buprenorphine is an antagonist/partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor (this is the putative antidepressant action of the combination drug). Samidorphan is an antagonist at the mu-opioid receptor, with tighter binding affinity than buprenorphine; hence, it prevents the mu-opioid analgesic effect of buprenorphine.

Rapastinel is being studied as an augmentation agent for treatment-resistant major depression. It received FDA fast-tracking on March 3, 2014, and has a novel mechanism of action by selectively binding as an antagonist/partial agonist at an allosteric site on the glycine binding region of the NMDA glutamate receptor. Rapastinel is administered intravenously and is a rapidly acting drug that demonstrates antidepressant as well as cognitive-enhancing properties likely related to its activity as an antagonist and partial agonist of the glycine binding site on the NMDA glutamate ion channel.

There has been increased interest in the role of inflammation in causing depression, exacerbating depression, and/or contributing to non-response in patients with treatment-resistant depression. Raison and colleagues6 looked at infliximab, a monoclonal antibody that inhibits the inflammatory cytokine tumor necrosis factor, in a cohort of 60 outpatients whose depression was moderately resistant to antidepressants. The subgroup of patients with elevated baseline levels of inflammatory biomarkers, including tumor necrosis factor and high-sensitivity C-reactive protein, demonstrated some improvement in their depressive symptoms compared with patients whose baseline levels of inflammatory biomarkers were not elevated.

Conclusion: looking forward to the next 100 years

MDD is a common and often disabling mental illness that has plagued humanity since the existence of historical records. The past 100 years has been a time of impressive advances in medicine, neuropsychiatry, pharmacology, and our understanding of the circuitry of the brain.

The birth of the monoamine hypothesis of depression in the early 1960s revolutionized our understanding of, and ability to treat, depression. However, full remission from a major depressive episode is hard to achieve, and even obtaining a 50% response in patients with depressive symptoms can be challenging.

All of our FDA-approved antidepressants have mechanisms of action that

(Continued on page 40)

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are grounded in the monoamine hypothesis. Over the past several decades, there have been exciting breakthroughs of novel mechanisms of action—all too often followed by disappointment after extensive basic science research and early-phase clinical trials. However, we must always look to the future with optimism. We never know when a new molecule discovered by serendipity or an idea coalescing in the mind of some graduate student will bear the fruit of our next paradigm-changing antidepressant.

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PSYCHIATRIST to work full-time in Manteca, CA. Must have CA medical license or ability to obtain. Send CV to MARK DAVID LEVINE, M.D. PSYCHIATRISTS PROFESSIONAL CORPORATION, 5835 N. Freeway Blvd., Ste 100, Sacramento, CA 95834 or email to: ProviderCV@cpsych.com.

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Psychiatrists who are looking for a good personal / work life balance are encouraged to consider joining Liberty Healthcare’s expanding group in California, Full & part-time outpatient, inpatient & medical director positions are available throughout San Diego, San Bernardino, Riverside & Kern Counties. Liberty offers outstanding compensation & benefits packages, no on-call, regular 40hr workweeks & ample time off.

For details, visit www.libertyhealthcare.com/careers or contact Carol Wertenly anytime at carol@libertyhealth.com / (610) 389-7437.

Outpatient Adult and Child Psychiatrists are needed for Stanislaus County Behavioral Health & Recovery Services, in the Central Valley less than two hours from San Francisco and Yosemite.

Recovery-oriented treatment provided in a multidisciplinary setting with friendly and dedicated staff members. Recently revised rates with full malpractice coverage and pension plan (PARS) as a Personal Service contractor with an income potential of over $325 K per year for adult psychiatrist and over $355 K per year for child psychiatrist for F/T work.

P/T options and the opportunity to combine Tele-Psych with limited onsite work are also available. Excellent work environment with NO Call Requirement, lower than average case load and comprehensive nursing & ancillary support makes this a very pleasant and rewarding opportunity. 31 applicants are welcome.

Fax CV to Viday Mukherjee, MD at (209) 558-4326 or Email: umukherjee@stanbhrs.org

STERLING CARE PSYCHIATRIC GROUP, INC. is a physician-owned practice group located in Ventura County, California. We are currently hiring psychiatrists to work in innovative programs throughout Ventura County Behavioral Health in Adult Services, Youth and Family Services and Quality Assurance. The ideal candidates are creative, energetic and comfortable working as part of a multidisciplinary team. Annual salary range is from $260,000 for board eligible to $353,600 for double boarded, bilingual child and adolescent psychiatrists. Generous benefits package includes performance bonus, health insurance, 401K with match, and up to 30 days of paid annual leave. 100% out of county defined benefit retirement plan.

Contact Tom Widroe at 805.680.7772 or tomwidroe@icloud.com

www.psychiatrictimes.com

December 13-15
Scottsdale, AZ
Hyatt Gainey Ranch

8th Annual National Update on Behavioral Emergencies

IBHI Full Day Seminar: Improving Care and Flow and Reducing Boarding for People With Behavioral Health Problems
See www.IBHI.Net

The only conference to address the behavioral emergencies in the acute care setting.
For emergency physicians, psychiatrists, psychologists, nurses, APNs, mental health workers, social workers, and physicians.

www.behavioralemergencies.com

CME Approval pending and CEUs available for RNs and SWs
Discounted registration rates for AABP members
Reduced fee for allied health, nurses, residents and students
For further information call Cyrene Wright at 773-257-6130
Cyrene.wright@sinaei.org
Course Director – Leslie Zun, MD, MBA at zumi@sinaei.org

Conference Sponsors

www.psychiatrictimes.com

Outpatient Psychiatry Opportunity
San Joaquin County Behavioral Health Services is seeking to fill Outpatient Adult [General], and Sub-Specialty Psychiatry (Child Psychiatry, Geriatric, Forensic, Addiction and Psychosomatic Medicine) positions in a multidisciplinary, recovery-oriented clinical setting. Services are provided either on-site or using a hybrid model of on-site and tele-psychiatry practice. The positions offer a very competitive salary with a guaranteed base, plus incentive opportunities, Board Certified Psychiatrists have the potential to easily earn over 300K+ a year with participation in the county defined benefit retirement plan. Also offered is an option to forego retirement participation earning 330K+ a year. Sub-Specialty trained physicians may have the potential to earn more. The compensation package includes comprehensive health insurance, deferred compensation plans, 30 days of paid time off that increase with tenure, and additional CME time. Signing and moving bonuses are also available. Interested J-1 and H-1B candidates are welcome to apply. Contact Khurram Durrani, MD at: kdurrani@sjcbhs.org; Fax CV to 209-468-2399. EOE.

Your Career in Paradise!
 Psychiatrist Job Opening In
 Santa Barbara, CA

Visit: http://www.getpsychhelpsb.com/
Contact Tom Widroe at 805.680.7772 or tomwidroe@icloud.com

Private Practice
Looking for the Freedom and Flexibility
Earn over $350K/Year
Choose your own hours
Clinical Freedom
Malpractice paid
H1 Visa Welcome

We are looking for Adult and Child Psychiatrists in San Francisco Bay Area
Los Angeles/Orange County Area
Sacramento Area

Comprehensive Psychiatric Services
Mansoor Zuberi, M.D.
(P) 925-944-9711 (F) 925-944-9709
drzuberi@gmail.com
www.psych-doctor.com

Child/Adult Psychiatry
This group offers major insurance contracts, strong referrals, scheduling, reimbursement, billing
Earning potential $200,000-300,000+, Option of starting part time or full time.
Contact info: fammin@gmail.com, Phone: 314-629-7696
Farzana Amin M.D. Medical Director
Heal Psychiatric Services, Inc.

www.psychiatrictimes.com

For additional California licensed telepsychiatrists. Contact us at 661-840-9270 or inquire with CV at jobs@telehealthdocs.com.

WestJEM

December 13-15
Scottsdale, AZ
Hyatt Gainey Ranch

8th Annual National Update on Behavioral Emergencies

IBHI Full Day Seminar: Improving Care and Flow and Reducing Boarding for People With Behavioral Health Problems
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The only conference to address the behavioral emergencies in the acute care setting.
For emergency physicians, psychiatrists, psychologists, nurses, APNs, mental health workers, social workers, and physicians.

www.behavioralemergencies.com

CME Approval pending and CEUs available for RNs and SWs
Discounted registration rates for AABP members
Reduced fee for allied health, nurses, residents and students
For further information call Cyrene Wright at 773-257-6130
Cyrene.wright@sinaei.org
Course Director – Leslie Zun, MD, MBA at zumi@sinaei.org

Conference Sponsors

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We offer high compensation packages in:
• Sacramento Area
• Greater Los Angeles Area
• Southern California
• San Diego County
• Imperial County, Mexico
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Our competitive compensation includes:
• Malpractice/Disability Insurance
• Paid medical license and DEA renewal fees
• 401K with 3% Contribution (after the first year)
• Health Insurance (including dental and vision)
• Four weeks of paid vacation & six paid holidays

Our benefits package includes:
• Paid time off
• 401K with 3% Contribution (after the first year)
• Health Insurance (including dental and vision)
• Four weeks of paid vacation & six paid holidays

Our competitive compensation packages vary from a minimum of $300,000 per year plus $10,000 in bonuses and a benefit package valued at approximately $90,000, to up to $500,000, for the industrious physician. Our generous benefit package includes almost 7 weeks paid time off per year. If you are creative and think outside the box, if you value diversity and cultural competency, if you like innovative programs that are patient driven, using a rehabilitative, rather than illness model, if you want more time to work with patients, to get the best results, then CEP America is the company for you. To learn more about the specific job openings and salary and benefit packages, check out our website at www.cep.com or Email your letter of interest and CV to our company President, Gary A. Hayes, Ph.D. at: Drhayes3@tbhcare.com

The doctors of TRADITIONS BEHAVIORAL HEALTH are the largest provider of MD psychiatric services to adult populations in institutional and community based programs in California. We provide services to the seriously and persistently mentally ill and have openings in the San Francisco Bay Area, Santa Barbara, San Diego and Los Angeles. Overall we plan to add 50 more Fulltime psychiatrists in California to bring our medical staff team to 400 psychiatrists. Our packages vary from a minimum of $300,000 per year plus $10,000 in bonuses and a benefit package valued at approximately $90,000, to up to $500,000, for the industrious physician. Our generous benefit package includes almost 7 weeks paid time off per year. If you are creative and think outside the box, if you value diversity and cultural competency, if you like innovative programs that are patient driven, using a rehabilitative, rather than illness model, if you want more time to work with patients, to get the best results, then CEP America is the company for you. To learn more about the specific job openings and salary and benefit packages, check out our website at www.cep.com or Email your letter of interest and CV to our company President, Gary A. Hayes, Ph.D. at: Drhayes3@tbhcare.com

TBH is an equal opportunity employer

For more information, visit: http://www.mirecc.va.gov/mirecc_fellowship.asp, or contact the Co-Director, Sherry Beaudreau, PhD, ARNP at Sherry.Beaudreau@va.gov or call (650) 493-5000, x64119.

Visit us online for a full list of psychiatric and tele-psychiatry opportunities.

CEP America
Be The Psychiatrist
You Are Meant To Be

CEP America is changing lives with innovative new programs. We are hiring part-time and full-time Emergency & Inpatient Psychiatrists in California:
• Greater Los Angeles Area
• San Francisco Bay Area
• Sacramento Area

Compensation
You become an equal and valued partner when you join the CEP America Partnership. We offer high compensation packages in addition to annual partner bonuses.

go.cep.com/Innovate2017
Visit us online for a full list of psychiatric and tele-psychiatry opportunities.

Silver times
December 2017
Office spaces available for Adult or Child Psychiatrist, Psychologist, FT/PT. Solo practitioner set up. Fee/Rent all inclusive (adm. support, billing, patient resources). No cap on income. We are located in San Diego. Contact: Office: (619) 258-6730 or ninisoffice@gmail.com; Paul Liederman MD (619) 871-9250

TLC Telecare Physician Services Organization

BE or BC psychiatrist needed. Following locations have immediate openings:
• San Jose, CA: Schedule: 40hrs per week. Pay Rate: $322,400. Benefits Eligible
• San Bernardino, CA: Schedule: 14hrs per week. Pay Rate: $183 per hour.
• Riverside, CA: Schedule: 9hrs per week. Pay Rate: $200 per hour (IC Rate)
• Oakland, CA: Schedule: 16hrs per week. Pay Rate: $156 per hour.
• Belmont, CA: Schedule: 16hrs per week. Pay Rate: $203 per hour (IC Rate)
• Ventura, CA: Schedule: 4hrs per week. Pay Rate: $208 per hour (IC Rate)

For additional listings, please visit: www.telecarecorp.com/psychiatrist-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 tlcrcruiting@telecarecorp.com

EOE M/F/V/Disability

Psychiatrist Position

J-1 Visa Opportunity in California

Imperial County Behavioral Health Services is currently recruiting for a full time psychiatrist. Imperial County is located 90 miles by freeway to the city of San Diego to the west, and 90 miles to Palm Springs to the north. Located in a rich farming area, Imperial County has a population of 180,000 and borders with Yuma, Arizona and with the cosmopolitan city of Mexicali, Mexico. Mexico population 1.2 million. San Diego State University maintains a satellite campus in Calexico and there are a number of private and public universities located in Mexicali, the state capital of Baja California Norte. Imperial County’s location and diversity make it the perfect place for a psychiatrist to relocate under the J-1 Visa program or for any reason.

The position pays a highly competitive salary, including health benefits for you and your family, and requires no hospital work and minimal after hours work freeing you up for more leisurely activities.

The successful candidate diagnoses and treats patients with mental, emotional, and behavioral disorders. Qualified candidate must have CA medical license or ability to obtain.

Send CV to Imperial County Behavioral Health Services, 202 North 8th Street, El Centro, CA 92243.

J-1 applicants welcome.

For additional information, please contact:

Marcy Sesma Lopez (442) 265-1605
marcyssesa@co.imperial.ca.us

PSYCHIATRIST

$246,900 - $323,000 annually
7 weeks of annual leave
Full benefits & retirement

Santa Clara Valley Health and Hospital System, a public healthcare system in the heart of Silicon Valley, is seeking BE/BC psychiatrists and 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

VA Advanced Fellowship Program in Mental Illness Research and Treatment

The Office of Academic Affiliations, Department of Veterans Affairs (VA), is accepting applications from physicians with residency training including but not restricted to psychiatry, neurology, and radiology, for its two-year Advanced Fellowship Program in Mental Illness Research and Treatment. The 24 Fellowship positions, across multiple sites nationwide, begin July 1st, 2018. Each Fellowship site is part of a VA research center or center of excellence, and is affiliated with an academic institution. This interdisciplinary program combines individualized, mentored research and clinical training with a state-of-the-art curriculum that emphasizes research methods, statistics, epidemiology, mental health systems, quality improvement methods, education, and service delivery. Fellowship sites are linked electronically for didactic efforts. Fellows devote the majority of their time to research and education activities and 25% to direct patient clinical care. Fellows develop and implement a research project, publish and present findings, participate in grant writing, and utilize the latest technology for educational activities and clinical service delivery. Applicants must have completed ACGME accredited residency training, be board eligible or board certified, and have an active, unrestricted U.S. license to practice. International medical graduates must also have a current visa and an ECFMG certificate that is valid indefinitely. The VA funds Fellows’ stipends in amounts based on previously completed ACGME accredited residency training.

For more information, visit: http://www.mirecc.va.gov/mirecc_fellowship.asp, or contact the Co-Director, Sherry Beaudreau, PhD, ARNP at Sherry.Beaudreau@va.gov or call (650) 493-5000, x64119.

www.sccnm.org
www.sccmhd.org

PSYCHIATRIST

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PSYCHIATRIST

$246,900 - $323,000 annually
7 weeks of annual leave
Full benefits & retirement

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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
**COLOMBIA**

The Department of Behavioral Health at Denver Health Medical Center is recruiting for a full-time Adult Psychiatrist to join our team on our expanding Outpatient Psychiatry Service. The Behavioral Health department at Denver Health (DH) is an integral part of a Level I 525-licensed hospital, where medical and surgical services are readily available, with a mission of providing quality health care for all citizens of Denver regardless of ability to pay. As Colorado’s primary safety net institution, DH has provided billions of dollars in uncompensated care.

We seek a psychiatrist who enjoys working in a team-based and multi-disciplinary approach to deliver compassionate, evidence-based psychiatric care for persons experiencing mental health crises.

Responsibilities include direct patient care, coordination with nurse practitioners, and teaching of medical students and psychiatry residents.

Applicants must be eligible for a Colorado medical license and be BE/BC in general adult psychiatry.

Providers interested in this opportunity should submit CV to: lawreen.mcbride@dhha.org

**FLORIDA**

**FLORIDA LIC, BE/BC CHILD / ADULT PSYCHIATRIST**

We are an extremely busy, upscale practice comprised of four psychiatrists, and twenty five psychologists, LCSW’s, and LMHC’s. We have two beautifully decorated offices in Boca Raton and Coral Springs Florida. If you are seeking an outstanding opportunity for a full-time private practice in a warm and friendly environment, we invite you to call Linda Berlin, Psy.D at (954) 227-2700 Option 1.

**Practice for Sale**

Busy established adult-outpatient practice in Jacksonville, FL. Includes office, furnishings, hardware, data and both business and medical software. Experienced staff available to continue with new owner.

www.drsgraybelle.com

203 523-7026

**CONNECTICUT**

**CLOSE TO HARTFORD AND NEW HAVEN - OUTPATIENT PSYCHIATRIST**

Seeking Adult Psychiatrist to work full-time on outpatient BH service in Bristol Hospital—a Magnet facility in Bristol, CT. Involves on-call coverage shared with other MDs and NPs for inpatient psych unit. Only 19 miles from Hartford; 30 miles from New Haven; and only 2 hours from NYC and Boston. Also, seeking Psychiatrists and PMHNPs for PT job and also weekend call for new geropsy unit opening in January 2018. Please contact Terry Good at 804-684-5661; email: terry.good@horizonhealth.com; Fax: 1-804-684-5663; EOE

**GEORGIA**

**Archbold Northside is a private, not-for-profit adult and geriatric inpatient behavioral health facility located in Thomasville, Georgia.**

Archbold Northside is currently seeking a full-time Psychiatrist and is dedicated to the stabilization and treatment of individuals suffering with acute mental illness and/or substance abuse issues. Designed for both comfort and privacy, our facility is located on a quiet, private, self-contained campus in Southwest Georgia thereby creating the perfect location for personalized, innovative, and compassionate treatment.

- **Call coverage: 1-4**
- **Generous healthcare plan and additional benefits offered**

**Contact Information:**

Jodie Hilson
Physician Recruiter
(229) 226-8018
jhilson@archbold.org

**HORIZON HEALTH**

Horizon Health is seeking a Medical Director for a 12-bed Geriatric and 30-bed Adult inpatient psychiatric service line in metro Chicago. The Medical Director provides program administration and oversight services regarding service line policies, practice, development, compliance, and performance improvement. Also provides training, supervision, and consultation to staff. Previous Medical Director experience and Board Certification required. Excellent compensation. For more information contact: Mark Blakeney, Vcye: 972-420-7473, Fax: 972-420-8233, email: mark.blakeney@horizonhealth.com EOE

**TELEPSYCHIATRY POSITION – needed for Adult Psychiatric Unit with fair number of geriatric patients in Harrisburg, IL.**

There is an onsite Psychiatrist and NP to share the work. Work with a top-notch BH team in a very supportive hospital. Must have IL medical license in good standing or be willing to get licensed.

Please contact Terry B. Good, Horizon Health, at 804-684-5661; email: terry.good@horizonhealth.com, Fax # 1-804-684-5663 EOE

**ILLINOIS**

**CHICAGO!**

Horizon Health is seeking a Medical Director for a 12-bed Geriatric and 30-bed Adult inpatient psychiatric service line in metro Chicago. The Medical Director provides program administration and oversight services regarding service line policies, practice, development, compliance, and performance improvement. Also provides training, supervision, and consultation to staff. Previous Medical Director experience and Board Certification required. Excellent compensation. For more information contact: Mark Blakeney, Vcye: 972-420-7473, Fax: 972-420-8233, email: mark.blakeney@horizonhealth.com EOE

**Assistant/Associate Professor of Clinical Psychiatry**

The Department of Psychiatry and Behavioral Medicine at the University of Illinois College of Medicine at Peoria is recruiting full-time faculty positions at the rank of Assistant or Associate Professor to join our expanding department. Two Clinician-Educator (CE) positions and one Psychiatry Residency Program Director (PD) position are open. Competitive applicants to the CE positions should value providing and teaching high-quality patient care and supporting the scholarship efforts of residents and medical students. The PD position is a planned changeover in leadership and available to applicants with experience and interest in educational administration and quality teaching. Highly competitive salary and benefits are commensurate with rank.

Responsibilities for the CE position include leading an interdisciplinary general psychiatry adult inpatient teaching unit composed of residents, medical students, nursing, social work and support staff. The PD position involves directing our 16-resident, ACGME-approved training program, promoting a culture of excellence, resident recruitment, teaching and resident evaluation. Other duties for both positions will be tailored to the interest of the applicant and include opportunities in adult and child outpatient clinics, partial hospitalization program, electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), community outreach, college student mental health, geriatric and forensic psychiatry, among others. Faculty members have protected time to pursue professional interests including clinical or educational program development or research. Our department values a positive, collegial culture and supports the growth, development and advancement of its members. The department has high faculty and resident satisfaction and low turnover.

Peoria and the surrounding Central Illinois area offer an attractive mix of small town charm and big city offerings. The large, diverse and supportive community is the area’s top employer. Peoria offers a diverse population, entertainment, arts, cuisine, low cost-of-living, excellent schools and an array of recreational activities with convenient access to larger cities such as Chicago, St. Louis and Indianapolis.

To inquire confidentially about a position, please contact Dr. Timothy Bruce, Search Chair, at (309) 495-1647 or tbjbruce@ucomp.uic.edu.

Minimum requirements: graduation from an ACGME-accredited psychiatry residency training program, board certification or board eligibility in general psychiatry and eligibility for unrestricted Illinois medical license. UIC is an EOE/AA/M/F/Disabled/Veteran employer. For fullest consideration, please apply by November 15, 2017 at the following link:

https://jobs.uic.edu/job-board/job-detail/33496315

The University of Illinois may conduct background checks on all candidates upon acceptance of a contingent offer. Background checks are performed in compliance with the Fair Credit Reporting Act.
**INDIANA**

**EVANSVILLE, IN – Ethnically Diverse City—Not too Large, Not too Small; Great Quality of Life: Excellent Schools — Medical Director position available on a 12-bed Adult Inpatient Psychiatric Unit in the St. Vincent’s Medical Center – an impressive hospital system in so IN. Hospital is flexible on the compensation package: employment with benefits; or for those more entrepre neurial minded, an independent contractor arrangement. Full-time or Part-time available. Join an outstanding behavioral team. Please contact Terry Good, Horizon Health, at 804-684-5661; terry.good@horizonhealth.com; Fax: 804-684-5663; EOE**

Excellent opportunity for adult psychiatrist interested in optimal setting for practice of community psychiatry; commutable from downtown Chicago in Merrillville, IN.

Regional Mental Health Center is a private non-profit mental health center that has successfully served Indiana for over 30 years. Experienced and collegial group of 12 mostly full-time psychiatrists, an extremely favorable practice environment. OP or IP work, call q 12 wks. Regional is a leader in psychiatrist-directed integrated care services. Highly full-time psychiatrists, an extremely favorable malpractice environment. OP or IP work in psychiatric service and will include participation in research. Core Faculty will model professionalism, collaboration and teamwork with staff and other health professionals. The faculty members are expected to engage in any or all areas of scholarship – discovery, teaching, integration, and application. Faculty members will contribute to the advancement of the discipline of Psychiatry as demonstrated by peer-reviewed funding; active participation in publication of original research or review articles in peer reviewed journals, or chapters in textbooks; publication or presentation of case reports or clinical series at local, regional, or national professional and scientific society meetings; or, participation in national committees or educational organizations.

The Uniformed Services University is an equal opportunity employer and is committed to increasing the diversity of the faculty. Applications from women and under-represented minorities are particularly encouraged.

**TENURE-TRACK ASSISTANT / ASSOCIATE PROFESSOR PSYCHIATRY**

**Department of Psychiatry Uniformed Services University**

The Department of Psychiatry and the Center for the Study of Traumatic Stress at the Uniformed Services University of the Health Sciences currently invites applications for a tenure-track Assistant / Associate Professor position. The Department desires a new faculty member to support education and training in psychiatry and behavioral health as well as expand ongoing research, animal and human, in: anxiety and stress (particularly acute stress responses, PTSD and dissociation); depression; behavior; and drug use. Individuals who hold an M.D. degree and have active fundable research are invited to apply.

The Uniformed Services University is located on the campus of Walter Reed National Military Medical Center in Bethesda, Maryland, adjacent to the National Institutes of Health and National Institutes of Mental Health and in close proximity to the biotechnology corridor in suburban Maryland. The area is rich in scientific opportunities and cultural offerings. Downtown Washington, D.C. is a short Metro ride away.

To learn more about the University, the Department of Psychiatry and the Center for the Study of Traumatic Stress, visit our websites at www.usuhs.edu/psy and www.cstsonline.org.

Candidates must be US citizens or permanent residents eligible for citizenship at the time of appointment. Interested individuals should submit a CV, brief statement of research interests (2-3 pages), and list of at least three (maximum of 5) references who are able to provide letters of reference (include name, title/position, and phone). These items should be submitted collective- ly in a single email to Dr. David Benedek through his Administrative Officer, Ms. Eliza Narvaez, at eliza.narvaez@usuhs.edu. Review of applications will begin on receipt and continue until the position is filled.

**NEW JERSEY**

**PSYCHIATRISTS**

for clinical staff and leadership positions

The State of New Jersey is seeking motivated BE/BC Psychiatrists for full time inpa- tient work in our Joint Commission Accredited state psychiatric hospitals and forensic center. Psychiatrists with manage- ment experience are also needed to serve as Medical Director or Associate Medical Directors in some facilities. Staff psychia- trists work with a multidisciplinary mental health team and are assisted by internists assigned to each unit. Competitive salary and excellent benefits package provided for full time positions. Voluntary paid on call opportunities also available.

**Hospital Locations:**
- Greystone Park Psychiatric Hospital, Morristown, NJ (Northern NJ)
- Trenton Psychiatric Hospital, Trenton, NJ (Central NJ)
- Ann Klein Forensic Center, Trenton, NJ (Central NJ)
- Special Treatment Unit, Avenel, NJ (Northern NJ)
- Ancora Psychiatric Hospital, Hammonton, NJ (Southern NJ)

**Candidates must possess:**
- N.J. medical license.
- Interested candidates should send cover letter and detailed resume to:
  - Robert Eilers, MD, Medical Director Robert.Eilers@dhs.state.nj.us

**POSITIONS IN NORTHERN NJ – Englewood:**
- Additional Psychiatrist needed on 12-bed geropsych unit and 9-bed adult unit for inpatient and consultation liaison work in Englewood Hospital. Can offer employment w/benefits. Jersey City: Outpatient position with some call responsi- bilities for inpatient adult psych unit. Bayonne: Outpatient position – 12 hours per week to start and then increasing from there. Hoboken: One weekend per month on-call position on adult and geropsych units. Please contact Terry B. Good at 804-684-5661; Email: terry.good@horizonhealth.com; Fax #: 1-804-684-5663; EOE

**Psychiatrist-PT**

Family Guidance Center of Warren County seeking PT psychiatrist(s) to work in our community behavioral health care center with adults with range of mental health and substance use disorders. 8 hours (Mon, Thurs) at our Phillipsburg office site.

Requirements: Board Certified (or eligi- ble) in adult psychiatry.

www.fgcwc.org

Send resume to the attention of Richard McDonnell rmcdonnell@fgcwc.org.

EOE M/F

**MISSOURI**

Compass Health operates facilities/clinics in forty-nine counties in rural Missouri and Louisiana where psychiatry services are needed

**OUTPATIENT PSYCHIATRISTS**

Immediate full-time positions available in the Compass Health System throughout Missouri and Central and Northern Louisiana (specific locations and openings are at www.compasshealthhome.org. Please specify acceptable locations on your CV.)

M.D. or equivalent professional degree, Missouri or Louisiana license eligibility, and Board Certification/Board Eligibility in Psychiatry are required.

Comprehensive benefits package and contract

Please submit CV to:

Cgrigg@compasshn.org

Fax: 417-532-6606

EOE

**NEW YORK**

**PSYCHIATRIST**

to join growing private practice in Northern Westminster, Putnam, Dutchess Counties, New York. This is an immediate need. Must be NYS licensed. Existing managed care affiliations a plus. Flexible hours, competent support staff. Can be FT or PT. Please send CV and letter of interest to jmsimonphd@gmail.com

c/o Carmel Psychiatric Associates

(203) 523-7026

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NEW YORK CITY & WESTCHESTER COUNTY

OSWEGO, NY – Great Work/Life Balance - College Town on Lake Ontario - 40 Miles from Syracuse – Outdoor enthusiasts’ paradise: numerous lakes, skiing options close on 40 minutes from the Thousand Islands; festivals and concerts almost every weekend throughout the summer. Seeking an additional Psychiatrist to work on a 28-bed adult inpatient psychiatric unit in the Oswego Hospital. Work with a great group of people in a very supportive hospital. Offering salaried position with benefits.

Please contact Terry B. Good, Horizon Health, at 804-684-5661; Fax: 1-804-684-5663; Email: terry.good@horizonhealth.com.

NORTH CAROLINA

SEEKING FULL TIME OR PART TIME CHILD & ADOLESCENT PSYCHIATRIST (BE/BC) to join an established, growing multispecialty group practice at our newly expanding office in Cary, NC. Out-patient only, fee-for-service, busy, no managed care, working with other psychiatrists, psychologists and educators in a family-oriented practice and community consistently rated as the top place to live in the country. Just minutes from RTP and 3 major universities. Flexibility in job, excellent collections and benefits. Email CV to Office Manager, Jyoti Gawi at jgawdi@fppa.com. Website: www.fppa.com

OHIO

FORTUNE 100 BEST PLACES TO WORK 6 YEARS IN A ROW – Full-time salaried position with benefits & sign-on bonus; open to Week on/Week off if two psychiatrists want to split the position. Southern OH Medical Center, Portsmouth, OH – 15-bed Geropsychiatric Unit. Top-notch program; top-notch staff; enjoy good work and a more laid back lifestyle.

Contact Terry Good, Horizon Health, 804-684-5661; terry.good@horizonhealth.com; Fax: 1-804-684-5663. EOE

(203) 523-7026

PSYCHIATRISTS
& PSYCH NURSE PRACTITIONERS

CONSULTATION SERVICES IN LONG TERM CARE (NH, SNF)

POTTSVILLE, PA – Seeking a Psychiatrist to work on the 36-bed Adult inpatient Psych Unit and 10-bed C/A Unit at the Lehighton Valley Hospital-Schuykill. Can offer part-time independent contractor work, or full-time employment with benefits. Also, a weekend call position is available as well if this is preferred. Please contact Terry B. Good, 804-684-5661; terry.good@horizonhealth.com; Fax: 1-804-684-5663. EOE

PENNСYLVANIA

The Penn State Health Milton S. Hershey Medical Center Department of Psychiatry is currently recruiting board eligible/certified psychiatrists for inpatient and outpatient positions in both adult and child psychiatry. We are a growing, vibrant department in a strong academic medical center. We host specialty clinical and research programs, including research that crosses the translational spectrum. Our educational programs include adult psychiatry residency, child fellowship, psychology internship, externship and post-doctoral fellows. We have a strong collaboration with basic and clinical science in other neuroscience disciplines across several Penn State campuses.

With our clinical partner, the Pennsylvania Psychiatric Institute, the Department staffs several outpatient and partial hospital programs for children and adults, 89 inpatient beds, ECT and other neuromodulation services, specialty sleep and eating-disorders programs, and expanding psychiatric consultation and integrated care programs for Hershey Medical Center.

Successful candidates should have strong teaching as well as clinical skills and, optimally, potential for scientific and scholarly achievement. We offer an attractive compensation package commensurate with qualifications. Tenure-track positions are possible. For consideration, send your CV to: Tami Tenbus, Physician Recruiter Phone: 717-531-5065 Email: ttenbus@hmc.psu.edu.

The Penn State Milton S. Hershey Medical Center is committed to affirmative action, equal opportunity and the diversity of its workforce. Equal Opportunity Employer – M/W/V/D

SOUTH CAROLINA

Psychiatrists who are looking for a good personal / work life balance are encouraged to consider joining Liberty Healthcare’s expanding group in South Carolina. Full & part-time outpatient, inpatient & telepsychiatry positions are available in Charleston, Columbia, Spartanburg & other locations throughout South Carolina. Liberty offers regular 40hr workweeks, no on-call, ample time off & assistance with licensing & relocation.

For details, visit www.libertyhealthcare.com/careers or contact Carol Wertley anytime at carolw@libertyhealth.com / (608) 261-1889; rlmunson@wisc.edu.

TEXAS

Growing Tele-Psychiatry Company seeks psychiatrists for all shifts.

Psynch Now is a physician owned Tele-psychiatry company based in Dallas, Texas and is currently recruiting for Texas Licensed Psychiatrists who are interested in making supplemental income from the comfort of home. Competitive pay, malpractice insurance covered and all needed equipment is provided. 24/7 coverage is needed in convenient day, evening and weekend shifts. Psynch Now provides services to behavioral health hospitals and acute care hospitals in the state of Texas.

You can visit our website at www.psynchnowus.com or call us at 1-844-635-2739

WISCONSIN

Psychiatry positions - Wisconsin

Our not-for-profit, university-based organization maintains the largest listing of child and adult Psychiatry positions in Wisconsin. We are currently aware of 25+ adult and C/A positions in both rural and urban communities statewide. Some are eligible for state/federal educational debt assistance. This is our 37th year of assisting psychiatrists with their job search here in Wisconsin. Most positions are with large, multi-specialty medical groups.

For a complete listing of all positions currently available here, please contact: Randy Munson, Wisconsin Office of Rural Health, University of Wisconsin School of Medicine & Public Health, Madison, WI, (608) 261-1889; rlmunson@wisc.edu

WISCONSIN

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& PSYCH NURSE PRACTITIONERS

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Excellent salaries, flexibility, autonomy, no call, comprehensive benefits. J-1 & H-1B Visa Waiver

Send CV to recruitment@medcarepc.com. Fax: (718) 239-0032; www.medcarepc.com

OSWEGO, NY – Great Work/Life Balance - College Town on Lake Ontario - 40 Miles from Syracuse – Outdoor enthusiasts’ paradise: numerous lakes, skiing options close on 40 minutes from the Thousand Islands; festivals and concerts almost every weekend throughout the summer. Seeking an additional Psychiatrist to work on a 28-bed adult inpatient psychiatric unit in the Oswego Hospital. Work with a great group of people in a very supportive hospital. Offering salaried position with benefits.

Please contact Terry B. Good, Horizon Health, at 804-684-5661; Fax: 1-804-684-5663; Email: terry.good@horizonhealth.com.

NORTH CAROLINA

SEEKING FULL TIME OR PART TIME CHILD & ADOLESCENT PSYCHIATRIST (BE/BC) to join an established, growing multispecialty group practice at our newly expanding office in Cary, NC. Out-patient only, fee-for-service, busy, no managed care, working with other psychiatrists, psychologists and educators in a family-oriented practice and community consistently rated as the top place to live in the country. Just minutes from RTP and 3 major universities. Flexibility in job, excellent collections and benefits. Email CV to Office Manager, Jyoti Gawi at jgawdi@fppa.com. Website: www.fppa.com

OHIO

FORTUNE 100 BEST PLACES TO WORK 6 YEARS IN A ROW – Full-time salaried position with benefits & sign-on bonus; open to Week on/Week off if two psychiatrists want to split the position. Southern OH Medical Center, Portsmouth, OH – 15-bed Geropsychiatric Unit. Top-notch program; top-notch staff; enjoy good work and a more laid back lifestyle.

Contact Terry Good, Horizon Health, 804-684-5661; terry.good@horizonhealth.com; Fax: 1-804-684-5663. EOE

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[contact information]