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KARACHI PSYCHIATRIC HOSPITAL

BULLETIN

(Psychiatric Research Articles)

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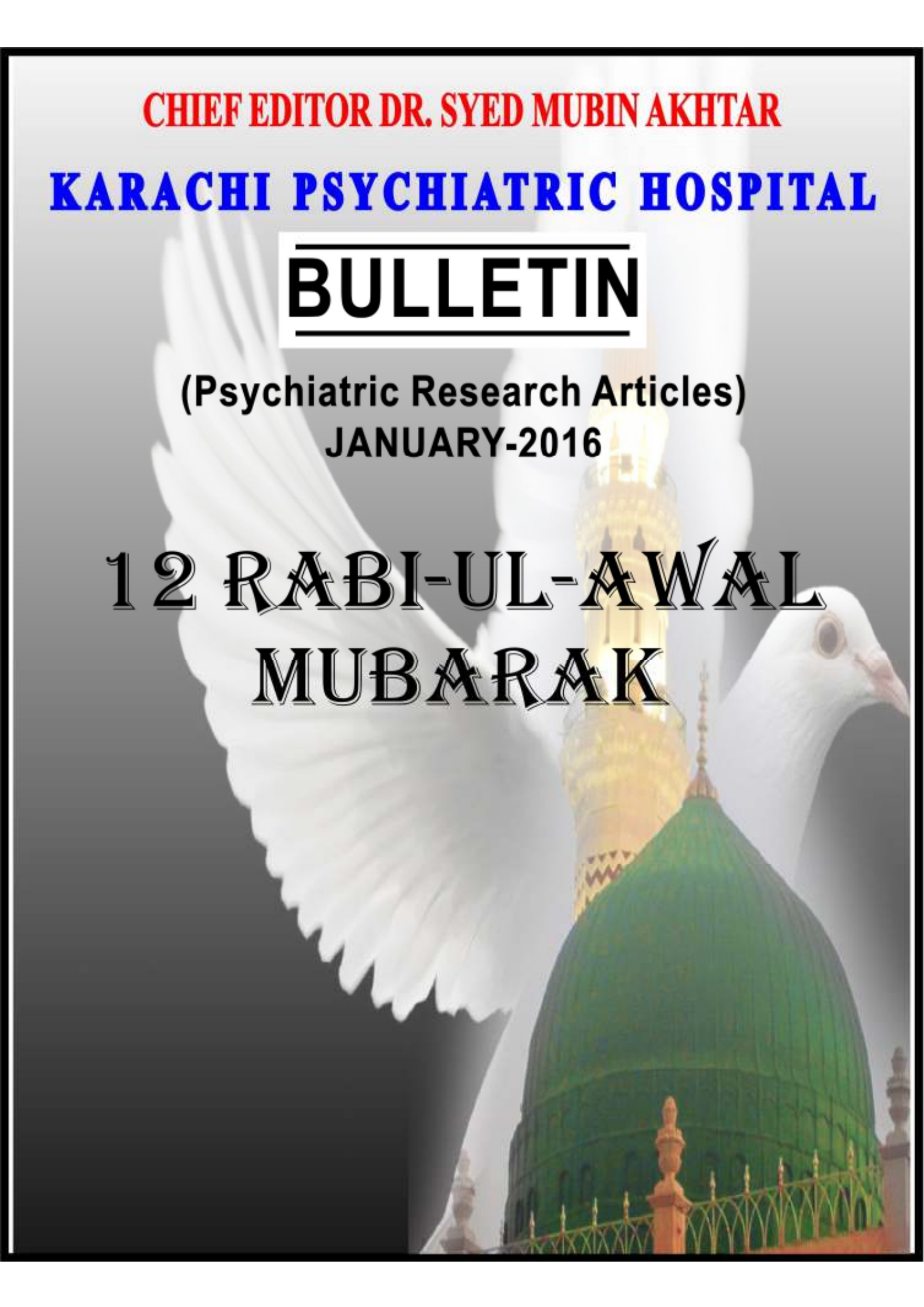
12 RABI-UL-AWAL MUBARAK



SCHOOL MEETING

16-11-2015

Syed Rashid Hasan Addressing the meeting

Principals and teachers are the Audience.

M.D. Karachi Psychiatric Hospital Dr. Syed Mubin Akhtar chairs a Meeting with Nine Adopted Govt. Schools' Principals (Happy Dale etc.)

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Human Screams Alter Amygdala Fear Pathways

Barbara Geller, MD reviewing Arnal LH et al. Curr Biol 2015 Aug 3.

This study identifies an acoustical characteristic shared by screaming and alarms — an insight that might clarify how parental verbal abuse leads to later psychopathology.

Although studies have supported the role of verbal abuse in later psychopathology (NEJM JW Psychiatry Aug 2006 and Am J Psychiatry 2006; 163:993), little was known about the physiology and brain circuitry associated with hearing screaming. To study screams, investigators examined acoustical characteristics of screaming compared with normal speech and music in several experiments (N=10–21 participants).

Screaming was found to occur in an acoustical temporal spectrum called roughness; this spectrum differs from the ones in normal speech that encode information about sentence meaning and a speaker's sex. When asked to rate the pleasantness of sounds, participants perceived screaming as unpleasant, even when compared with normal speech of similar loudness. When prompted to pinpoint sound location, participants had the greatest accuracy and quickest response for screams; the more unpleasant the scream, the earlier its location was identified. On functional magnetic resonance imaging, screams activated amygdala circuits that were not activated by non-rough sounds.

Long Work Hours Are Associated with Excess Risk for Coronary Heart Disease and Stroke

Bruce Soloway, MD reviewing Kivimäki M et al. Lancet 2015 Aug 19.

Encouraging or requiring people to work longer hours could have substantial public health implications.

Two meta-analyses of published cohort studies have suggested that long working hours lead to excess risk for coronary heart disease (CHD). To explore this hypothesis further, researchers combined data from 25 prospective cohort studies from Europe, the U.S., and Australia that included data on working hours and incident CHD or stroke. The resulting data sets included more than 600,000 people who were followed for a mean 8.5 years for CHD and more than 500,000 people who were followed for a mean 7.2 years for stroke.

Compared with standard working hours (35–40 hours weekly), and after adjustment for age, sex, and socioeconomic status, long working hours (>55 hours weekly) were associated significantly with higher risk for incident CHD (relative risk, 1.13) and stroke (RR, 1.33). Risk for incident stroke increased linearly as working hours increased; no such dose-response relation was seen for CHD. Excess risk for CHD with longer working hours was more pronounced in patients with low than with high socioeconomic status; no other significant subgroup differences were found.

Migraine Surgery: A Solution for a Common Problem?

Neurology Times
Veronica Hackenthal, MD
News | August 07, 2015 | Headache and Migraine
By Veronica Hackenthal, MD

When medications no longer offer relief to your patients with migraines, surgical treatment may be the answer.

Migraines affect about 43% of women and 18% of men over the course of their lifetimes. In the US, medical costs due to migraine are estimated at $1 billion, with $16 billion lost in productivity per year. Medical management is often ineffective. Botox is FDA approved for treating migraines but usually offers only temporary relief.

Study 1: Decompression of Trigger Points

• Surgical treatment is based on the premise that peripheral sensory branches of the trigeminal and cervical spinal nerves become compressed and irritated, causing migraine.
• Surgery focuses on decompression of four main trigger points: frontal, temporal, nasoseptal, and occipital.
• As of October 2014, 17 clinical studies, including 2 RCTs, supported the efficacy of surgical decompression for migraines, with the overall success rate approaching 90%.
• Most common adverse events: transient numbness at the surgical site, incisional hair loss, intraoperative bleeding, transient uneven brow movement.

Study 2: Migraine Trigger Site Deactivation

• A migraine trigger site, where the migraine begins, is defined by anatomical areas innervated by branches of the trigeminal or occipital nerves.
• Compression of the nerve at these sites and irritation of surrounding structures can lead to inflammation and migraine.
• A recent study looked at 20 adult patients with bilateral temporal migraines.
    ♦ Patients received unilateral surgical decompression and unilateral neurectomy (on the opposite side) of the zygotemporal branch of the trigeminal nerve between January 2011 and August 2012.
    ♦ 19 patients completed the study at 12 months followup.
• After surgery:
    ♦ 34/38 (89%) operative sites showed >50% improvement in migraine frequency, days, severity, and duration.
    ♦ 21/38 (55%) operative sites showed complete resolution of symptoms.
    ♦ No statistically significant difference was found between decompression vs neurectomy for decreased migraine frequency, days, severity, and duration.
    ♦ No major complications occurred.
• Conclusion: "Both avulsion neurectomy and decompression of the zygotemporal branch of the trigeminal nerve are equally effective methods for the treatment of temporal migraine headache... Performing decompression as the first option leaves avulsion neurectomy as another option if decompression fails to provide the intended relief. It is our recommendation that whenever feasible, decompression should be attempted first."

Migraine Symptoms for Decompression vs. Neurectomy

	Frequency per month	Days per month	Severity	Duration (hours)	Migraine Headache Index Score
Decompression Group	Decreased from 14.6 to 2.2	Decreased from 14.1 to 2.3	Decreased from 7.0 to 2.9	Decreased from 9.6 to 4.8	Decreased from 42 to 2.9
Neurectomy Group	Decreased from 14.2 to 1.9	Decreased from 6.8 to 2.6	Decreased from 6.8 to 2.6	Decreased from 10.1 to 5.3	Decreased from 41 to 2.5

1. Migraine Headache index score = migraine frequency x duration x intensity

Study 3: Migraine Surgery in Adolescents

• Migraine among adolescents is common, often not adequately controlled, and has been linked to psychosocial problems like anxiety and depression.

• Topiramate is the only FDA approved drug for migraine prevention in adolescents, approved for ages 12-17.

• A recent retrospective review looked at the surgical outcomes for one surgeon, Bhaman Guruyon, who pioneered migraine surgery.

• The study included all adolescent patients ≤18 years with a family history of migraine into adulthood, and neurologist confirmed refractory migraine.

• Legal guardians completed a migraine headache questionnaire preoperatively and at each postoperative visit.

• Analysis included 14 patients and 15 operations (11 girls, 3 boys, average age 16 years, average followup 38.2 months).

• One year followup after surgery:

- ♦ Migraine frequency and migraine days per month both decreased from 25 to 5 ($P < 0.0001$).
- ♦ Migraine index decreased from 148.1 to 12.4 ($p < 0.001$).
- ♦ Duration (number of hours/24 hours) decreased from 0.71 to 0.25 ($p = 0.002$).
- ♦ Migraine severity decreased from 8.2 to 4.3 ($p = 0.0004$).
- ♦ Five patients reported complete resolution of all migraine symptoms.
- ♦ One patient showed no improvement in frequency of migraine, but severity and duration did improve.
- ♦ No surgical complications were noted.

• Conclusion: "In the adolescent population with migraine headaches refractory to traditional medical management, migraine surgery may offer symptomatic improvement of migraine headache frequency, duration, and severity in patients with identifiable anatomical trigger sites."

Take Home Points

• Migraine is a common problem, especially in women; medications and botox may not treat the underlying disorder.

• Surgical treatment is based on the premise that peripheral sensory branches of the trigeminal and cervical spinal nerves become compressed and irritated, causing migraine.

• Studies suggest that surgical decompression for migraine may have an overall success rate approaching 90%.

• Neurectomy and decompression of the zygotemporal branch of the trigeminal nerve may be equally effective for treating temporal migraines.

• Surgical decompression may be effective for treating certain adolescents with migraine.

Studies Provide Little Support for Guidelines on Dietary Fats and Supplements

By Larry Husten

Two new studies demonstrate the shaky underpinnings of guidelines that encourage the intake of omega-3 fatty acids.

The first, a large meta-analysis in the Annals of Internal Medicine, examined dietary fatty acid consumption, fatty acid biomarkers, and fatty acid supplements. Among the chief findings:

- Omega-3 and omega-6 fatty acids: There were trends for modest benefits associated with dietary intake or supplements, but these did not achieve statistical significance.
- Saturated fatty acids: There was no discernible effect of total saturated fat as measured by either dietary intake or circulating biomarkers.
- Monounsaturated fatty acids: No effect was found.
- Trans dietary fats: A harmful effect was confirmed.

In the second study, published in JAMA Internal Medicine, 4200 patients with age-related macular degeneration were randomized to omega-3 fatty acids; lutein/zeaxanthin (carotenoids found in the eye); both; or placebo. After roughly 5 years, there was no significant reduction in cardiovascular outcomes in the treatment groups.

Commentators say it's now clear that omega-3 supplements "with daily doses close to 1 g in patients with or without established CVD shows no clear, considerable benefit." They conclude that for now, omega-3s should be prescribed only for patients with severe hypertriglyceridemia, "an extreme minority of the general population."

Adapted from CardioExchange

Depression and Risk for Cardiovascular Disease

Thomas L. Schwenk, MD reviewing Whooley MA et al. JAMA 2008 Nov 26.

Physical inactivity might partly explain the association.

Depression is a significant predictor of the development, recurrence, and prognosis of cardiovascular disease (CVD). To identify the mechanisms that mediate this association, California researchers recruited 1017 patients (mean age, 67) with known stable CVD (e.g., angiographic evidence of coronary artery disease or revascularization, history of myocardial infarction, exercise-induced ischemia). All were assessed for depression, cardiac status, and 31 behavioral and biologic risk factors; 199 patients had symptoms of moderate-to-severe depression.

After roughly 5 years of follow-up, 341 CVD events occurred, including new-onset heart failure, MI, stroke, and transient ischemic attack. The age-adjusted risk for a CVD event was 10% per year for depressed patients and 6.7% per year for nondepressed patients. When the difference in incidence rate was adjusted for each of the behavioral and biological risk factors, adjustment for physical inactivity resulted in the largest decrease in the risk differential. After adjustment for all medical comorbidities and cardiac status, depressed patients had a statistically significant 31% greater risk for a CVD event than nondepressed patients. After further adjustment for C-reactive protein levels and physical inactivity, the difference in risk was eliminated.

Predicting Schizophrenia Before It Starts

Joel Yager, MD reviewing Chan MK et al. Transl Psychiatry 2015 Jul 14.

In high-risk individuals, panels of molecular biomarkers and psychological screening combine to predict subsequent schizophrenia with reasonable sensitivity and specificity.

Only about 30% of individuals with defined prodromal syndromes develop full-blown schizophrenia. In this first-ever, three-stage approach, researchers identified a panel of biomarkers (ultimately refined to 22 serum-based proteins involved in various metabolic, inflammatory, and immune processes) capable of predicting subsequent schizophrenia. Some researchers are industry-employed.

In the first stage, biomarkers were identified that distinguished 331 first-episode, drug-naive patients with schizophrenia from controls. Second, the biomarkers were validated in two cohorts totaling 181 individuals (combined totals: schizophrenia patients, 93; controls 88).

Finally, the biomarkers were used to predict subsequent-onset schizophrenia in two other cohorts. One cohort comprised 185 U.S. military personnel initially without psychiatric symptoms who presented with schizophrenia or bipolar disorder within 30 days following blood collection and 184 controls. In this cohort, 24 proteins predicted schizophrenia (but not bipolar disorder) with sensitivity of 88% and specificity of 81%. The second cohort comprised 76 help-seeking prodromal youth, 50 of whom met Comprehensive Assessment of At-Risk Mental State (CARMMS) criteria for "ultra-high risk," of whom 14 subsequently developed schizophrenia. (Of the 26 not initially classified as "ultra-high risk," 4 subsequently developed schizophrenia as well.) In this cohort, 22 proteins predicted subsequent schizophrenia with sensitivity of 89% and specificity of 66%. Adding positive-symptom subscores from CARMMS yielded 89% sensitivity and increased specificity to 79%, far better values than achieved with CARMMS scores alone.

Using the Internet to Increase Access to Evidence-Based Treatment for Obsessive-Compulsive Disorder

Psychiatric Times
Sapana R. Patel, PhD
Andrew B. Schmidt, LCSW, PhD
H. Blair Simpson, MD, PhD
August 25, 2015 | Obsessive Compulsive
Disorder, Anxiety, Psychopharmacology , Telepsychiatry
By Sapana R. Patel, PhD, Andrew B. Schmidt, LCSW, PhD, and H. Blair Simpson, MD, PhD
Internet-based CBT has shown promise to improve access to therapy for patients with OCD, which is associated with a profoundly diminished quality of life and social isolation.
BRIEF COMMUNICATION
In recent years, the increasing number of computer and Internet users has greatly expanded the potential to access evidence-based care for the treatment of psychiatric disorders. Computer-assisted and Internet-based treatments expand accessibility of treatment for individuals who may have economic, transportation, or other restrictions that limit access to face-to-face services. Furthermore, these programs have the advantages of increasing cost-effectiveness of evidence-based treatments by reducing contact time with a therapist, broadening client participation in therapy-based activities in real-world settings, and monitoring quality of care and client progress. Researchers have developed programs that range from self-directed therapy based on "self-help" models to therapist-supported interactive treatments with or without video conferencing. Much of the research on computer or Internet-based programs has been focused on anxiety disorders. Given the severe and disabling nature of obsessive-compulsive disorder (OCD), numerous efforts have been made to improve access to evidence-based treatment for those facing barriers to care.
OCD is associated with a profoundly diminished quality of life, social isolation, and a substantial economic burden on society; the lifetime prevalence of OCD is 2%. It is characterized by the presence of persistent and distressing thoughts and worries—obsessions—and repetitive or ritualized behaviors—compulsions. Most often the compulsions are carried out in direct response to the obsessions and serve to reduce anxiety and distress.
Evidence-based guidelines identify 2 types of effective treatments of OCD: medications, including SNRIs (eg, clomipramine) and SSRIs, and cognitive-behavioral therapy (CBT) consisting of exposure and response prevention (ERP). With ERP, patients gradually expose themselves to their fears or obsessions while refraining from engaging in rituals or compulsions.

Exposures are conducted in a systematic fashion starting with situations that are least feared and gradually working toward situations that are most feared. Despite the documented efficacy of ERP, few patients receive this treatment in clinical practice, although many patients prefer CBT to medication alone and CBT is superior to antipsychotic medications as an augmentation strategy for those experiencing residual symptoms. Barriers to care include uncertainty about where to seek treatment, lack of trained therapists, shame and stigma associated with mental health problems, time limitations, competing demands, and costs associated with seeking psychological care.

Multiple efforts have been made to improve access to CBT for patients with OCD; among these, an Internet-based CBT (I-CBT) for OCD, developed at the Karolinska Institutet in Sweden, is the most promising program developed to date. In I-CBT, individuals use an Internet-based treatment platform to learn about their illness and to engage in ERP under the confidential guidance of an expert therapist. I-CBT overcomes many barriers to care and allows individuals to receive evidence-based ERP treatment under the guidance of trained therapists without the traditional restrictions and requirements of face-to-face meetings.

In one trial, I-CBT was found to be far superior to a control treatment (response to treatment: 60% for I-CBT vs 6% for control); I-CBT also had low dropout rates (12%), comparable to rates seen in face-to-face treatment. Moreover, decreases in OCD severity with I-CBT are comparable to those with face-to-face ERP. I-CBT is a clear advance over other self-help programs because it is a single, integrated system of treatment supported by a therapist accessible anywhere via the Internet. This program has the potential to substantially affect public health and enable underserved OCD patients to access evidence-based care. However, I-CBT has never been tested outside of Sweden in diverse OCD patient populations and settings. It is exciting to see effects of I-CBT in Sweden, and we look forward to seeing how such a program might fare in the US. This type of innovation could change how we treat anxiety disorders, including OCD.

Disclosures:

Dr Patel is Research Scientist at the New York State Psychiatric Institute and Assistant Professor of Clinical Psychology in the department of psychiatry of Columbia University, College of Physicians and Surgeons, New York (for information about a pilot research study on I-CBT, you can contact Dr Patel at Sapatel@nyspi.columbia.edu). Dr Schmidt is Clinical Researcher at the New York State Psychiatric Institute. Dr Simpson is Director of the Anxiety Disorders Clinic and Center for OCD and Related Disorders at the New York State Psychiatric Institute and Professor of Psychiatry at Columbia University, College of Physicians and Surgeons. The authors report no conflicts of interest concerning the subject matter of this article.

The Anxious Bipolar Patient

Psychiatric Times
September 06, 2011 | Bipolar Disorder, Anxiety
By Kavital Lohano, MD and Rif S. El-mallakh, MD
Linked Articles
The Anxious Bipolar Patient
Substance Use Disorders in Patients with Anxiety Disorders
Anxiety Disorders with Comorbid Substance Abuse
Issues in Treating Anxiety Disorders in Pregnancy
Exposure Therapy for Anxiety Disorders

Bipolar disorder is a clinically challenging condition. In addition to the multiple mood states that patients can experience, the illness is frequently associated with multiple comorbid medical and psychiatric conditions. Bipolar disorder can best be understood as a family of related disorders that share core features of mood or affective variation, impulsivity, propensity toward substance abuse, and predisposition to other psychiatric conditions. Most patients who have bipolar disorder have a coexisting anxiety disorder. These include generalized anxiety disorder (GAD), social phobia, panic disorder, and PTSD. Anxiety disorders, by themselves or in combination with a mood disorder, are associated with an increased risk of suicide and psychosocial dysfunction.

The prevalence of comorbid bipolar and anxiety disorders (with the exception of simple phobias) is high in youths. For example, it is at least twice as high as comorbid anxiety and disruptive behavior disorders. GAD and separation anxiety are the anxiety disorders most commonly associated with bipolar disorder. In children with type I bipolar disorder, comorbid anxiety predicted greater dysfunction, manifested by earlier onset of bipolar disorder and more frequent psychiatric hospitalizations.

A comorbid anxiety disorder in bipolar patients greatly complicates the presentation, the interpretation of symptoms, and the treatment of bipolar disorder, and it negatively alters the prognosis.

Anxiety disorders comorbid with bipolar disorder

Panic disorder. In the Epidemiologic Catchment Area (ECA) study of the early 1990s, 21% of patients with bipolar disorder had comorbid panic disorder. This is a 26-fold higher incidence than in the general population. Panic disorder and bipolar disorder may share a special relationship with each other. A study of bipolar probands and their siblings found that panic disorder travels with bipolar disorder exclusively and rarely occurs independently of bipolar disorder. This unique relationship may be mediated by a genetic predisposition that resides in chromosome 18.

Obsessive-compulsive disorder (OCD). In both the ECA study and the more recent National Comorbidity Survey, the incidence of OCD was 10-fold greater in bipolar patients than the general population. The risk of OCD is greater in family members of bipolar probands, which suggests a familial or genetic association. However, episodic obsessive-compulsive symptoms may simply be a variant of how bipolar disorder is expressed and not a true comorbidity. Either

way, the relationship between bipolar disorder and OCD frequently has its origins in childhood and yields a greater burden of anxiety symptoms.

Posttraumatic stress disorder. PTSD may have a special relationship with bipolar disorder because both mania and depression may be perceived as traumatic or because events in the course of the illness may increase the risk of severe traumatic events. Consequently, PTSD may be over 6 times more likely to occur in bipolar patients than in the general population. The co-occurrence of PTSD with bipolar disorder lowers quality of life, increases rapid cycling and suicide attempts, and reduces the likelihood of remaining well.

Social anxiety. Despite frequent grandiose or expansive behavior during mania, most patients with bipolar disorder actually suffer from social phobia—a potential contributor to dysfunction in bipolar patients.

Comorbidity and outcomes

The combined burden of bipolar and anxiety disorders nearly always has a deleterious effect on outcomes. Comorbid illness is associated with marked increases in symptom burden that includes greater risk of psychosis, earlier age at onset of psychiatric symptoms, worse treatment response and more treatment resistance, impaired quality of life, increased suicidal ideation and actions, and increased substance abuse. Whether the poor prognosis is due to an interaction between the two conditions or to the additive burden is unknown.

Accurate diagnosis of comorbid anxiety disorder and bipolar disorder is important. The cost of care increases when a bipolar patient is treated exclusively for anxiety because of a misdiagnosis. Once a dual diagnosis has been made, effective treatment may be challenging.

Treatment of anxiety disorders

Antidepressants. Serotonergic antidepressants have shown efficacy as acute and prophylactic treatment for all anxiety disorders and are considered first-line agents. This is generally true whether the serotonergic effect is alone, is associated with noradrenergic reuptake inhibition, or is obtained by reuptake or monoamine oxidase inhibition. Non-serotonergic antidepressants (specifically bupropion) do not appear to be particularly effective.

In bipolar patients, antidepressants have the potential to induce mania, destabilize the course of illness by increasing bouts of mania and depression, and induce a chronic depressive state. The risk of these complications is higher if the bipolar patient receives antidepressants during periods of euthymia or over long periods. Use of antidepressants specifically for anxiety in bipolar patients would be expected to be associated with more complications. This may account for the observation that pharmacological treatments of comorbidities, such as anxiety disorders, in bipolar patients are generally underused, whereas psychosocial services are used more frequently by patients with coexisting anxiety disorders.

Antipsychotics. Second-line pharmacotherapy for anxiety becomes first line in bipolar patients with anxiety disorder. Specifically, studies of atypical antipsychotics such as quetiapine have shown that these agents reduce anxiety in social anxiety disorder and GAD. Although the patients recruited for these studies did not have a mood disorder, quetiapine monotherapy (300 to 600 mg/d) significantly reduced anxiety and depressive symptoms in patients with bipolar disorder. Quetiapine may be of questionable benefit in patients with PTSD. While open-label,

uncontrolled studies support use of this agent for PTSD, there were more early discontinuations with quetiapine than with prazosin and, thus, long-term benefit was lost.

At doses below 4 mg/d, risperidone does not appear to be helpful for the treatment of anxiety symptoms in patients with bipolar disorder. Augmentation of mood stabilizer treatment with risperidone was also ineffective.

The olanzapine/fluoxetine combination is approved for the treatment of bipolar depression. It may be useful in the treatment of comorbid anxiety as well. However, olanzapine alone has minimal effect.

Anticonvulsants. There are no randomized controlled trials that examine the use of anticonvulsants for the anxiety component in bipolar patients. However, anticonvulsants appear to have a small effect in reducing anxiety. In a small open-label study, more than 40% of patients with GAD (without mood disturbance) saw at least a 50% improvement in symptoms with valproate. Similarly, modest benefit was seen in a group of patients with PTSD who received divalproex in an open-label study. Unfortunately, when the effect size is small in open-label studies, it suggests that results of blinded studies are likely to be negative.

Alternative agents. Gabapentin has been shown to be effective for social phobia in a randomized placebo-controlled trial. This effect on anxiety is probably what underlies the early reports of gabapentin efficacy in bipolar disorder. The related anticonvulsant, pregabalin, is also useful in social phobia and GAD at higher doses (approximately 600 mg/d). These agents have not been studied in bipolar patients with anxiety but are probably safe to use in this patient population.

Benzodiazepines are clearly effective in many different types of anxiety disorders. However, their use is problematic, and these agents must be prescribed cautiously.

Nonpharmacological approaches. Psychotherapy may be the treatment of choice for patients with anxiety disorders in general. For example, CBT is as effective as medications in the acute management of panic disorder. Unlike medications, the effect lasts long after treatment has ended. However, there are no randomized controlled trials for psychotherapy in bipolar patients who have comorbid anxiety. Nonetheless, therapies such as CBT and relaxation training may be useful in bipolar patients.

Summary

Anxiety disorders are commonly comorbid with bipolar disorder and are responsible for much of the morbidity associated with this condition. Treatment of anxiety can be a challenge, since the mainstay of treatment—serotonergic antidepressants—may adversely affect the course of bipolar disorder. Although other agents are available, there is a dearth of information on the outcomes of anxiety treatment for bipolar patients.

Clinicians generally must apply the results of studies performed in patients who have anxiety disorders without mood disturbance to their bipolar patients. This is a reasonable practice, although it is far from ideal. The field needs more high-quality research studies to define the best practice options in treating patients with comorbid anxiety and bipolar disorders.

Managing Anxiety in the Medically ill

Psychiatric Times
January 30, 2015 | Special Reports, Anxiety, Comorbidity In
Psychiatry, Psychopharmacology, Psychotherapy
By Yu Dong, MD, PhD, Fatima Noorani, MD, Rushi Vyas, MD, Chandrika Balgobin, DO, Vanessa Torres-Llenza, MD, and Catherine Crone, MD
Linked Articles
Does TMS Hold Promise for Generalized Anxiety Disorder?
Treating Comorbid Anxiety Disorders in Patients With Schizophrenia: A New Pathway
Managing Anxiety in the Medically Ill
Pharmacological Strategies for Generalized Anxiety Disorder
Anxiety is a fundamental aspect of the human experience. It can be an adaptive response to a perceived threat, with both psychological and physiological features. In the short term, anxiety can be a motivator and prepare one to confront a crisis. When anxiety persists or occurs abnormally, it can impair functioning and lead to an anxiety disorder. In the medical setting, anxiety can be a normal coping mechanism when dealing with the stress of illness. However, if it exceeds social, psychological, or physiological needs, anxiety can become maladaptive—leading to somatic symptoms that cause distress and impairment.
Prevalence of anxiety in the medically ill
Patients with primary anxiety disorders, such as generalized anxiety disorder (GAD), panic disorder, and phobias, as well as PTSD, report a higher rate of certain medical illnesses than are observed in the general population. The National Comorbidity Survey Replication showed a 12-month prevalence rate of 3.1% for GAD and a lifetime prevalence rate of 5.7%; the lifetime prevalence for panic disorder was found to be 4.7%, with a 12-month prevalence of 5.7%. In comparison, the general prevalence of GAD in primary care is thought to be 8%. Findings from Fleet and colleagues suggest that an estimated 25% of 441 chest pain complaints in an emergency department (ED) setting were due to panic attacks.
Specific medical phobias, such as fear of blood, needles, or MRIs (due to claustrophobia), are quite common. Combined blood-injectioninjury phobias have been found to have a lifetime prevalence of over 3% in a general population sample. The presence of these phobias is of concern because they can contribute to patients having difficulty in pursuing medical care.
The lifetime prevalence of PTSD is 6.8%, with a 12-month prevalence estimated to be 3.5% in the general population.1 In a primary care setting, 12% of patients examined were found to have PTSD; 30% to 40% of motor vehicle accident survivors were found to have PTSD, so were 20% to 45% of burn victims. The diagnosis of an acute distress disorder strongly predicted the presence of PTSD 6 months later. Although PTSD and acute stress disorder are categorized under trauma and stressor-related disorders in DSM-5, in this article, PTSD is considered as a primary anxiety disorder.
Impact of anxiety disorders on medical illness
Anxiety disorders cause diminished functioning and well-being along with increased suffering; these effects are amplified in the presence of comorbid medical illness. As a group, they

contribute to symptom severity in medical populations, functional impairment, and increased risk of disease progression. Anxiety also plays a role in increased health care use and cost, greater number of iatrogenic complications, and decreased adherence to treatment.

Beyond psychosocial implications of anxiety disorders, there are also physiological effects of anxiety. Anxiety can create excessive sympathetic activation, alteration in inflammatory response, and disruption of the hypothalamic-pituitary-adrenal axis—predisposing patients to increased health risks. Comorbid anxiety disorders and medical illnesses often lead to a self-perpetuating cycle in which a chronic medical illness negatively affects level of function, leading to depression and anxiety, which, in turn, can worsen the underlying medical condition. The dynamic interplay between comorbid anxiety disorders and medical illnesses can pose diagnostic and management challenges.

Primary anxiety disorders and comorbid physical illnesses

Patients with primary anxiety disorders are more likely to suffer from GI, respiratory, cardiac, and neurological disorders, even after adjusting for confounding factors such as sex, depression, and substance use disorders. Among patients with panic disorder, GAD, and PTSD, rates of irritable bowel syndrome are much higher than in those with no psychiatric diagnoses. Similarly, panic disorder, GAD, and phobias are strongly associated with asthma and cancer. Anxiety disorders are associated with an increased incidence of cardiovascular disease, such as myocardial infarction, angina, sudden cardiac death, and hypertension, and frequent panic attacks are associated with worse cardiac outcomes. PTSD is associated with increased risk of cardiovascular disease, increased rates of re-hospitalization, and decreased adherence to treatment regimens. Primary anxiety disorders, particularly panic disorder, are also comorbid with seizure disorder. Finally, social anxiety disorder and panic attacks are often seen in patients with Parkinson disease.

Secondary anxiety and secondary anxiety disorders

Since there is a bidirectional relationship between anxiety and medical illnesses, many severe medical conditions can lead to secondary anxiety that ranges from normal psychological reactions to illness to intense anxiety or preoccupation about somatic sensations, which result in impaired functioning. A diagnosis of a severe, chronic, or debilitating medical illness will invariably elicit a number of negative emotions, such as anxiety, fear, sadness, and anger. When the emotional reactions are out of proportion to the context and lead to significant impairment in functioning, secondary anxiety disorder (ie, adjustment disorder with anxiety) can be the result.

DSM-5 conceptualizes adjustment disorder as a stress-response syndrome that occurs after exposure to a distressing event and is listed under traumaand stressor-related disorder. Secondary anxiety can also result from the effects of substance use, either from intoxication or withdrawal from a drug or anxiety as an adverse effect of a medication. lists agents that may cause anxiety.

Anxiety secondary to general medical conditions

Some medical disorders, such as pheochromocytoma and hyperthyroidism, can produce anxiety directly by affecting neuroendocrine systems. Other medical disorders produce anxiety indirectly through autonomic arousal that the patient interprets as a psychological state, such as anxiety experienced during an acute myocardial infarct or pulmonary embolism..

Anxiety as an impersonator of medical illness

Anxiety can be camouflaged as somatic symptoms to mimic a medical illness, especially in the primary care setting. Some of the somatic expressions of anxiety include tachycardia, palpitations, sweating, flushing, dry mouth, dizziness, tremor, muscle tension, headaches, and fatigue. These symptoms could present as a "false alarm" because of an underlying anxiety disorder or a somatoform disorder. The somatic component complicates the overall picture and results in more functional impairment and higher use of medical resources.

There is a major revision of somatoform disorders in DSM-5. Psychological factors affecting medical conditions is a new diagnosis under the classification of somatic symptom and related disorders. Psychological factors include psychological distress, patterns of interpersonal interaction, coping style, and maladaptive health behaviors. In DSM-5, individuals with high health anxiety and significant somatic symptoms are given a diagnosis of somatic symptom disorder; this replaces somatization disorder in DSM-IV. Alternatively, individuals with high health anxiety without somatic symptoms may receive a diagnosis of illness anxiety disorder, which replaces hypochondriasis in DSM-IV.

Diagnostic and management challenges

The anxious patient in the medical setting can be diagnostically challenging. A key component to the clinical approach toward an anxious patient is differentiating pathological anxiety from a regular emotional response. If an anxious response is disproportional to a medical illness or illness exacerbation, etiologies for anxiety need to be investigated systematically using a bio psychosocial approach.

Biologically, acute anxiety may be the first sign of exacerbation of an underlying illness, an undiagnosed medical condition, or substance intoxication or withdrawal. To aid in diagnosis, the patient examination includes a detailed history; focused physical examination; complete review of medications; collateral information; and diagnostic testing, such as toxicology screens. For example, a patient with a history of myocardial infarction may present to the ED with panic attacks along with palpitation and numbness. The treating physician must first rule out recurrent cardiac abnormalities, pulmonary issues, new-onset neurological abnormalities, medication or substance intoxication/withdrawal, and other conditions that require immediate interventions.

Psychologically, an anxious reaction to a medical illness may be due to a patient's uncertainty regarding a medical diagnosis or prognosis. In the medical or surgical ward, factors that contribute to anxiety include being unfamiliar with the hospital setting, staff, and procedures. From a social perspective, fears about losing functional capacity or becoming overly dependent on others may be a contributing factor; fear of death is another source of anxiety. Involvement of family and social supports can provide greater reassurance in these situations.

Managing acute anxiety pharmacologically differs significantly from managing chronic anxiety disorders. Benzodiazepines are effective for acute anxiety and ideally should be limited to short-term use. Lorazepam is commonly used for anxiety-induced chest pain or anxiety associated with chest pain. Patients with cancer comorbidities may benefit from benzodiazepines because they also help with nausea and insomnia. Benzodiazepines should be used with caution in patients with a history of substance abuse and in the elderly who have cognitive impairment and who may be at risk for falling. Benzodiazepines can also decrease respiratory drive in patients with obstructive sleep apnea and severe chronic obstructive pulmonary disease (COPD).

Low-dose atypical antipsychotics (such as quetiapine, risperidone, and olanzapine) are effective in acute debilitating anxiety that causes obsession, disorganized thinking, and overwhelming distress and that interferes with medical care; however, there is no well-designed study of this class in the treatment of anxiety. Mirtazapine, an α2-antagonist and serotonin antagonist, has been found to work quickly and effectively for acute anxiety associated with insomnia and poor appetite. Orally disintegrating tablets of mirtazapine, clonazepam, olanzapine, and risperidone are available and may be helpful for patients with dysphagia or with a diet restriction. Some of the benzodiazepines and atypical antipsychotics also have oral solution and injectable forms, which are very useful in acute medical and surgical settings.

In outpatient clinics, a patient's anxiety may arise from a perceived negative self-image in the physician's eyes. This example may be particularly pertinent in situations in which patients either caused or exacerbated their illness (eg, tobacco use). Excessive worry in these situations may contribute to reluctance in following up with health care appointments, and to denying or failing to disclose information that ultimately leads to treatment delays or less optimal treatment. Therefore, while firm reminders are appropriate, harsh critique of the patient is unwarranted and may contribute to poorer treatment adherence.

SSRIs are the first-line agents for chronic anxiety disorders and are generally well tolerated by elderly patients. Sertraline, citalopram, and escitalopram have fewer drug-drug interactions than paroxetine and fluoxetine.9 Sertraline has the most evidence of safety and effectiveness in patients with significant cardiovascular disease.

SNRIs, such as duloxetine and venlafaxine, are FDA-approved for primary anxiety disorders and neuropathic pain. Buspirone, a partial serotonin-2 agonist, is recommended for chronic anxiety in the elderly and in patients with COPD, sleep apnea, or substance abuse. Buspirone is a category B drug for pregnancy and thus is not expected to harm an unborn baby; the other anxiolytic agents are classified under category C or D.

Anticonvulsants and β-blockers can be used for both acute and chronic anxiety. Valproic acid is used for anxious agitation seen in patients with traumatic brain injury, mental retardation, or advanced dementia. Gabapentin, a γ-aminobutyric acid (GABA) analogue, is not only effective in patients with acute GABAergic withdrawal anxiety but is also used off-label for chronic anxiety, such as panic disorder and PTSD. Pregabalin can be considered for social phobia and GAD. β-Blockers reduce the sympathetic surge of anxiety, as seen in performance anxiety and social phobia[4]; they are also the first-line treatment for akathisia as an acute form of anxiety.

Psychotherapy is also effective for managing anxiety in the medically ill. Supportive therapy and brief cognitive-behavioral therapy can be readily used at bedside or in an office. Psychodynamic psychotherapy is an option for those patients who are more resilient and whose condition is less acute. Other therapies, such as hypnosis, meditation, and biofeedback, can play a role in both anxiety and physical symptoms.

Treatment modalities should be discussed with the patient to ensure autonomy, minimize the subjective feeling of losing control, increase adherence, and ultimately strengthen the therapeutic alliance. Collaboration with other treatment teams is essential in reducing health care utilization.

Does TMS Hold Promise for Generalized Anxiety Disorder?

Psychiatric Times
January 30, 2015 | Special Reports, Anxiety, Neuropsychiatry, Transcranial Magnetic Stimulation

By Gretchen J. Diefenbach, PhD and John W. Goethe, MD

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Treating Comorbid Anxiety Disorders in Patients with Schizophrenia: A New Pathway

Managing Anxiety in the Medically Ill

Pharmacological Strategies for Generalized Anxiety Disorder

Generalized anxiety disorder (GAD) is a chronic psychiatric condition defined by excessive and uncontrollable worry, occurring more days than not for at least 6 months, and accompanied by at least 3 of 6 hyperarousal symptoms (restlessness, muscle tension, fatigue, irritability, difficulty in sleeping, concentration problems). Lifetime prevalence in the general population is 5.7%, and rates are higher in treatment-seeking samples such as primary care and psychiatric outpatients. GAD commonly co-occurs with other disorders, most often depression, which further complicates presentation and prognosis. The burden of GAD is substantial. At the individual level, GAD is associated with significant quality-of-life impairments and diminished physical health. At the systems level, GAD is associated with high use of health care services and high costs.

Pharmacotherapy (antidepressants and/or anxiolytics) is the most common treatment for GAD; cognitive-behavioral therapy (CBT) is the method of counseling with the strongest empirical support. Pharmacotherapy and CBT are superior to placebo, but one-third to half of patients do not achieve symptom remission. Since even the best existing treatments leave many GAD patients without relief, alternative treatments are needed.

Neuromodulation is a novel psychiatric treatment that targets specific brain circuits as a means to improve psychopathology. Transcranial magnetic stimulation (TMS) is the neuromodulation therapy with the largest research base and the only one of several such therapies with an FDA-approved indication for treatment-resistant MDD.

In the FDA-approved protocol, the magnet is applied to the scalp over the left dorsolateral prefrontal cortex (DLPFC) to deliver a series of high-frequency pulses intended to stimulate areas implicated in MDD. The efficacy of these stimulation parameters for depression has been supported in numerous clinical trials, and research suggests that anxiety symptoms in patients with MDD also improve. However, there has been far less research on using TMS to treat

anxiety disorders and very little is known about use of TMS in GAD. (See Machado and colleagues for an in-depth review.)

Neurobiology of GAD

The rationale for considering TMS for GAD is based on neurobiological models of the disorder. GAD is characterized by abnormalities in the frontal and limbic structures as well as in the connectivity between these regions. The frontal regions most often implicated in GAD are the prefrontal cortex and anterior cingulate cortex, and the limbic region most often studied is the amygdala: increased attention has recently been directed toward the hippocampus. Although there are some inconsistencies across studies, structural abnormalities, as well as decreased structural and functional connectivity between frontal and limbic regions, have been documented in GAD patients.

Functional neuroimaging further supports the hypothesis that GAD is characterized by inefficient biological mechanisms associated with emotion regulation. During worry induction, there is increased activation in the prefrontal cortex and decreased activity in the amygdala in both GAD patients and nonanxious control participants; however, unlike nonanxious control participants, GAD patients are not able to normalize this neural activity following worry induction.

The results from studies that use tasks that require conflict monitoring and emotion regulation (although somewhat inconsistent) support a model of GAD characterized by hypoactivation in the prefrontal cortex and anterior cingulate cortex indicative of deficient top down emotional control.

Although there are many possible neuromodulation targets to improve emotion regulation, this article focuses on the potential role of stimulation of the DLPFC, the region most often targeted in depression and the only region yet tested in patients with GAD. The DLPFC plays a central role in emotion regulation processes as a structure responsible for maintaining task goals and interacting with other brain regions to maximize goal attainment. TMS affects not only the stimulation target but also other cortical and subcortical regions with which it has connections.

Key regions in the regulation of anxiety that may be influenced by cascading effects of DLPFC stimulation are the dorsal anterior cingulate cortex (responsible for threat appraisal and conflict/error monitoring); the inferior frontal gyrus (implicated in risk aversion and selective inhibition); and the ventral anterior cingulate cortex and ventral medial prefrontal cortex, which integrate inputs from cortical regions and suppress limbic activity (through the uncinate fasciculus pathway to the amygdala and bed nucleus of the stria terminalis). Therefore, DLPFC stimulation may improve anxiety via enhanced functioning of and/or improved communication within fronto-limbic networks.

Findings from nonclinical samples indicate that neuromodulation of the DLPFC alters anxiety-related cognitive biases, risk aversion, and cortisol secretions, all of which are implicated in GAD pathology. These data support a potential role for neuromodulation of the DLPFC in

changing emotion regulation of anxiety, but the ways in which the DLFPC exerts an influence are not known. Proposed biological mechanisms of DLPFC stimulation in patients with depression include normalization of neuroendocrine, neurotransmitter, and/or neurotrophic factors, which may also play a role in anxiolytic effects of TMS, given that abnormalities in these systems have been implicated in GAD as well.

Neuromodulation treatment for GAD

The only published study of TMS for GAD was a small open-label trial in adults.Treatment consisted of 6 sessions (delivered twice weekly for 3 weeks) of low-frequency (ie, inhibitory) stimulation over the right DLPFC. There was a 60% response rate (defined as a 50% or more improvement in the Hamilton Anxiety Rating Scale [HARS] total score) and a 60% remission rate (defined as HARS score less than 8) at post-treatment; results were largely maintained over a 6-month follow-up.

A recently published case study used transcranial direct current stimulation (tDCS), another form of neuromodulation, to treat GAD in a 58-year-old woman. In tDCS, a direct electrical current is applied to the scalp to alter cortical excitability, with anodal stimulation to excite and cathodal to inhibit. The tDCS parameters were set with the cathode over the right DLPFC and the anode over the contralateral deltoid.

Fifteen treatments were administered (5 sessions weekly for 3 weeks). Self-reported anxiety symptoms were in the nonclinical range at post-treatment and follow-up, indicating acute and sustained remission of symptoms. Clinician-rated symptom changes were not reported, however, which prevented cross-study comparisons. In addition, although the outcomes reported are encouraging, only limited conclusions can be drawn given the absence of a control group.

At the 2014 American Psychiatric Association meeting, preliminary results of a randomized controlled trial (RCT) in GAD patients who received either active TMS or placebo (using a “sham” coil) were presented.18 Low-frequency stimulation was applied to the right DLPFC for a total of 30 sessions (5 sessions weekly for 6 weeks). Preliminary data show that more than two-thirds (71%) of the active TMS group were treatment responders (50% or greater improvement in HARS score), while only one-quarter of the sham group met this criterion.

At the 3-month follow-up, responder rates were maintained in those who were receiving active repetitive TMS (rTMS). Also, nearly half (43%) of the patients in the active TMS group had symptom remission (HARS score less than 8) at post-treatment, with some additional gains in remission rates over the 3-month follow-up. Remission in the sham group was achieved by only 1 patient and only at post-treatment.

Preliminary analyses from this RCT in patients with GAD suggest that DLPFC activation during a symptom provocation task (used to induce stressful uncertainty) increases following active rTMS stimulation but not following sham stimulation. Data from a study with healthy control participants suggest that DLPFC neuromodulation alters activation of, and functional

connectivity between, the DLPFC and ventral medial prefrontal cortex during decision making. More research is needed to determine the effect of TMS on neurocircuitry in GAD.

Clinical challenges

Currently, there is a limited empirical base to support clinical decision making. There is no FDA-approved indication for neuromodulation therapies for GAD and, thus, any use of TMS to treat GAD is off-label. Optimal stimulation parameters are unknown. In the trials of TMS for GAD, 1-Hz stimulation was applied for 15 minutes to the right DLPFC (900 pulses per session) at an intensity of 90% of the passive motor threshold. However, the number of sessions differed substantially (6 vs 30 sessions).

It will be important to determine which TMS treatment parameters are best for GAD, including consideration of brain regions other than the DLPFC. When targeting the DLPFC, the standard procedure for coil placement is 5 cm rostrally from the patient's motor cortex (identified with a motor-evoked potential). However, this procedure results in a minority of patients fitted optimally. Neuronavigation—either structural or functional—allows more individualized precision and improves the efficacy of TMS in treatment of depression. However, this technology is not available in most clinical settings.

There are also no data to identify which GAD patients are most likely to benefit from TMS. Some candidate predictors to explore include enhanced anterior cingulate cortex and attenuated pretreatment amygdala activation, which both predict response to pharmacotherapy and/or CBT for GAD. Cerebral blood flow to the ventral medial prefrontal cortex, which predicts response to low-frequency right DLPFC stimulation in depressed patients, might also be studied as a predictor of TMS response in GAD. Lastly, the only data for TMS in GAD have been from adults. There is evidence that the neurobiology of GAD changes with age; therefore, it will be important to determine whether adjustments are needed when applying TMS across the life span.

Conclusions

Available data suggest that TMS holds promise as a treatment for GAD, but larger and more definitive clinical trials are needed. In addition, it is important for future research to determine the optimal treatment parameters and predictors of treatment response. The mechanisms by which TMS exerts an anxiolytic effect are poorly understood, but hypotheses can be generated and tested based on neurobiological models of GAD and emerging data about the role of TMS in treating this disorder.

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Treating Comorbid Anxiety Disorders in Patients with Schizophrenia: A New Pathway

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By Amélie M. Achim, PhD, Stephanie Sutliff, MSc, and Marc-André Roy, MD, MSc
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The presence of anxiety disorders in persons with psychotic disorders is gaining increased attention. The evolution of the diagnostic criteria in the different editions of DSM has contributed to an increased awareness of these comorbidities. For instance, in DSM-III an anxiety diagnosis could be given only if anxiety was clearly "not due to" another Axis I disorder, while in DSM-III-R and DSM-IV, diagnosis was allowed if anxiety was "unrelated to" or "not better accounted for by" the main diagnosis, respectively. While such criteria allow a comorbid anxiety disorder diagnosis in persons with schizophrenia, overlaps between the symptoms of anxiety disorders and those of psychosis may complicate the application of these hierarchical rules.

While the diagnostic criteria have not changed significantly from DSM-IV to DSM-5, the latest revision of DSM provided an opportunity to discuss the potential benefits of a dimensional approach rather than a categorical approach to diagnosis. While the implementation of such a dimensional approach was judged premature given its potential impact on clinical practice, these discussions emphasized that patients can present with symptoms that cross the established diagnostic boundaries.

Using a meta-analysis, we identified high rates of anxiety disorders in patients with schizophrenia—38.3% of patients presented with at least one anxiety disorder. The mean prevalence for individual anxiety disorders ranged from 5.4% for agoraphobia to 14.9% for social anxiety disorder.

Another striking finding from this meta-analysis was the puzzling variations in rates reported between studies. For instance, rates for obsessive-compulsive disorder (OCD) varied from 0.6% to 55%. While some partial explanations for these variations were uncovered, they remained largely unexplained. Nonetheless, the meta-analysis allowed us to highlight several factors that could contribute to increased detection of anxiety disorders in schizophrenia. For example, social anxiety disorder, OCD, and panic disorder were more often identified in outpatients than in inpatients. This finding suggests that these disorders are easier to assess and to distinguish from symptoms of psychosis once acute symptoms have abated.

Comorbid anxiety disorders were typically more prevalent in studies that assessed diagnoses with the Structured Clinical Interview for DSM (SCID) and those that supplemented the SCID with additional scales that targeted the anxiety symptoms. The latter method of assessment had a significant effect, particularly for social anxiety disorder, OCD, and PTSD.

In a recent study, we used a comprehensive semistructured interview that included all SCID-IV questions as well as the questions from the Liebowitz Social Anxiety Scale and from the Yale-Brown Obsessive Compulsive Scale to identify anxiety symptoms in outpatients with recent-onset psychosis (M. A. Roy, MD, MSc, et al, unpublished data, 2014). The study comprised 80 outpatients with recent onset of a schizophrenia spectrum disorder, 53% of whom also had a current anxiety disorder; the lifetime prevalence was 60%.

In 48% of patients, DSM-IV criteria for a social anxiety disorder were met; however, 41% of these patients had not spontaneously reported social anxiety symptoms when asked using the SCID gate questions about social anxiety (unpublished results). These cases were only detected when questions from the Liebowitz Social Anxiety Scale were added. This supports the idea that asking more specific questions can uncover some unsuspected anxiety symptoms. Anxiety comorbidity may be overlooked when basic clinical methods are used, but identification of anxiety symptoms and anxiety comorbidity may be facilitated by using targeted questions, such as those of anxiety scales, and may also be facilitated in stabilized patients.

It is increasingly recognized that positive outcome for patients with schizophrenia should not be limited to controlling the positive and negative symptoms of the disorder, but should aim to help patients achieve good functioning and quality of life. Identifying comorbid anxiety disorders as potential treatment targets may contribute to more positive outcomes. For instance, an increase in the rate of suicide attempts and poorer functioning have been reported for schizophrenia patients who present with comorbid anxiety disorders.

Pharmacotherapy

In schizophrenic patients with comorbid anxiety, antipsychotics are typically supplemented with medications that target anxiety; alternatively, in some patients, a switch is made to another antipsychotic. Data that support the efficacy of these treatments are limited and consist mainly of small open-label trials and case reports. We are aware of only one randomized controlled study by Reznik and Sirota, which included 30 inpatients with schizophrenia who exhibited symptoms of OCD. The patients received fluvoxamine in addition to their current antipsychotic. They had a significant decrease in symptoms, without any significant psychotic relapse. Similar findings for fluvoxamine were also seen in 2 case reports. Nowadays, in clozapine-treated patients, other SSRIs would be favored, given the strong interaction between clozapine and fluvoxamine caused by cytochrome P-450 inhibition, which may lead to toxic blood levels of clozapine.

Clomipramine as a supplement to antipsychotic medication has been successful in reducing symptoms of OCD, but it has been associated with an exacerbation of psychosis in some patients. Other add-on medications that improve symptoms of OCD in schizophrenia include lamotrigine; milnacipran; and SSRIs other than fluvoxamine, such as escitalopram, sertraline, and fluoxetine.

Although most studies have focused on comorbid symptoms of OCD, in patients who exhibit social anxiety symptoms, switching the current antipsychotic to aripiprazole improved symptoms of social anxiety and psychosis and also improved functioning. Adding alprazolam or imipramine to an antipsychotic or switching the current antipsychotic to quetiapine has been shown to reduce panic symptoms in patients who present with schizophrenia and comorbid panic disorder.

CASE VIGNETTE

Christian is a 21-year-old who is seen a few months after experiencing a first psychotic break. He has responded well to monotherapy with 15 mg/d of olanzapine, but he is convinced that some of his thoughts have been put into his head by an unknown outside force. His psychiatrist asks him about the origins of this preoccupation. Christian describes a silly, repetitive sentence that kept popping into his mind—a sort of mantra—that happened before his psychotic break: he was aware that it originated with him and tried to resist it. During the psychotic episode, he developed a delusional belief about the origin of this mantra.

On further questioning, he described signs of an undiagnosed Tourette disorder during his adolescence, a condi-tion closely related to OCD. After an explanation that this repetitive thought could be an obsession, he agreed to citalopram supplementation, titrated to 30 mg/d. Shortly thereafter, the repeti-tive thought and its delusional explanation disappeared.

Anxiety symptoms as a consequence of antipsychotics

Pharmacotherapy for anxiety symptoms in patients with schizophrenia presents unique challenges: antipsychotic treatment may play a role in the exacerbation of anxiety symptoms in these patients. Such an association has been reported with antiserotonergic antipsychotics, primarily clozapine.

An observational study of 543 patients reported a higher prevalence of OCD in patients treated with clozapine (38.9%) than in those treated with olanzapine (20.1%) or risperidone (23.2%), or than in those not taking antipsychotics (19.6%). The study similarly showed that symptoms of OCD were even more prevalent when clozapine was taken for 6 months or longer. OCD may also be particularly prevalent in patients with schizophrenia who receive higher doses of clozapine, or in those who present with symptoms after the initial administration of the drug.

While some symptoms of OCD have been identified as related to the introduction of an antipsychotic medication, it is unlikely that drug effects fully account for the higher rates of OCD or other anxiety disorders in patients with schizophrenia for the following reasons:

• An increased prevalence of anxiety disorders, particularly OCD, predates the neuroleptic era

• Symptoms of OCD can be present before the onset of psychosis

• Anxiety disorders are frequent in clinical high-risk samples and can predict psychosis, which suggests that the anxiety was present before the introduction of medication

Since patients treated with clozapine differ from those treated with other drugs on a broad array of indicators of severity, it is premature to conclude that clozapine is a genuine causative factor for OCD. Given the well-proven efficacy of clozapine in decreasing psychotic symptom severity in treatment-resistant patients, combining treatment with aripiprazole or sertraline may be warranted to control anxiety symptoms.

Nonpharmacological approaches

Cognitive-behavioral therapy (CBT) can be effective in reducing anxiety symptoms in patients with schizophrenia. An open-label trial and a case study, which focused on psychological treatments for OCD in patients with schizophrenia, reported improvement following CBT. The efficacy of group CBT for social anxiety in patients with schizophrenia is supported by 2 randomized controlled studies. In these studies, the researchers randomly assigned schizophrenia

patients with social anxiety disorder either to group CBT or to a waitlist. They documented significantly greater improvements of social anxiety for the CBT group.

One randomized controlled study reported improvement of PTSD symptoms following CBT in a large group of patients with major mental disorders and PTSD (N = 108). Four open-label trials also support the efficacy of CBT for improving PTSD symptoms in patients with schizophrenia. Finally, promising results were reported for improvement of panic disorder in patients with schizophrenia using CBT.

A variety of other nonpharmacological approaches have also been proposed for the management of anxiety in patients with schizophrenia (eg, yoga, meditation, relaxation), but they have not specifically targeted comorbid anxiety disorders. Thus, the extent to which these results may apply to anxiety stemming from psychosis or comorbid anxiety disorders is unknown. These approaches may require some adaptations for their use in patients with psychotic syndromes.

Our clinical experience, illustrated in the following case vignette, suggests that simple psychoeducation, particularly if given shortly after the onset of symptoms, may prevent full-blown OCD.

CASE VIGNETTE

Felix is an 18-year-old with psychotic symptoms that warranted a diagnosis of schizophrenia, because the symptoms persisted during an inpatient stay of several weeks despite recreational drug abstinence (verified with regular urine checks). Because of an insufficient response to 2 antipsychotics, clozapine was introduced. His symptoms and his functioning both improved. However, Felix asks for a dosage increase because his “crazy ideas are coming back.” He describes having homosexual urges whenever he meets one of his close friends and fears that his friend may become aware of these ideas.

He is advised not to try to resist the thoughts; rather, he should accept that they are there. Eventually he agrees that if he does not appear worried, nobody will have a clue about these thoughts. During the following 3 months, he reports some recurrences of the thoughts, but they rapidly vanish when he ignores them.

Conclusion

Given the limited empirical evidence from randomized trials, it is difficult to make strong recommendations about either pharmacological treatment or psychological treatment for comorbid anxiety disorders in patients with schizophrenia. However, given the impact of these comorbid conditions on health outcomes, addressing them can certainly be beneficial for patients.

The accumulating evidence warrants an individualized approach—adding an SSRI or another drug while carefully monitoring the results. CBT also seems to provide interesting advantages to control anxiety symptoms, with strong evidence for social anxiety and emerging evidence for other disorders. although there are basic guidelines for treatment strategies, taking into account the patient’s specific needs is fundamental in treating these comorbidities.

Excess Risk for Intracranial Hemorrhage with Concurrent Antidepressants and NSAIDs

Paul S. Mueller, MD, MPH, FACP reviewing Shin J-Y et al. BMJ 2015. Mercer SW et al. BMJ 2015.

Patients who take both nonsteroidal anti-inflammatory drugs and antidepressants should be monitored for bleeding.

Use of either antidepressants or nonsteroidal anti-inflammatory drugs (NSAIDs) is associated with excess risk for upper gastrointestinal bleeding; risk is even higher when these drugs are used concurrently. Moreover, a 2012 meta-analysis showed a small excess risk for intracranial hemorrhage (ICH) in patients who received selective serotonin reuptake inhibitors (NEJM JW Psychiatry Dec 2012 and Neurology 2012; 79:1862), but whether concurrent use of antidepressants and NSAIDs poses additional risk for ICH is unknown. In this retrospective, propensity score–matched cohort study, Korean researchers compared risks for ICH in 4.1 million new users of antidepressant drugs who did or did not concurrently use NSAIDs.

After adjustment for multiple variables (e.g., dementia, anticoagulant use), risk for ICH within 30 days after initiating an antidepressant was significantly higher in patients who received concurrent NSAIDs than in those who did not (hazard ratio, 1.6). No differences in risks for ICH were observed among various antidepressant drug classes. In subgroup analysis of patients with concurrent prescriptions, risk for ICH was higher in men than in women (HRs, 2.6 and 1.2, respectively).

Drug Treatments for Diabetic Neuropathy: A Meta-Analysis

Allan S. Brett, MD reviewing Griebeler ML et al. Ann Intern Med 2014 Nov 4.

Randomized trials are plentiful, but the evidence as a whole has substantial limitations.

A new systematic review and network meta-analysis of drug therapies for painful diabetic neuropathy has been published. The reviewers discovered 65 relevant randomized trials involving 27 medications, with nearly 13,000 participants. Key findings are as follows:

- Serotonin-norepinephrine reuptake inhibitors (SNRIs), topical capsaicin, tricyclic antidepressants (TCAs), and anticonvulsants all reduced pain compared with placebo.
- As a group, SNRIs and TCAs reduced pain more than did anticonvulsants and capsaicin.
- Very few studies extended beyond 3 months' duration.
- For individual drugs, carbamazepine, venlafaxine, duloxetine, amitriptyline, and pregabalin[1] were statistically superior to placebo.
- Few head-to-head comparisons of individual drugs exist, and most showed insignificant differences between drugs; however, pregabalin was inferior to venlafaxine and duloxetine.
- Side-effect profiles differ among these drug classes; adverse effects were problematic with virtually all of them.

Psychotic Depression: Underrecognized, Undertreated—and Dangerous

Psychiatric Times
Barnett S. Meyers, MD
July 31, 2014 | Special Reports , Depression , Mood Disorders
By Barnett S. Meyers, MD

Here: the history of psychotic depression for the Study of the Pharmacotherapy of Psychotic Depression (STOP-PD), a summary its epidemiology, significance, diagnostic complexity, and treatment, as well as case vignettes.

This article describes the history of this diagnostic construct for the Study of the Pharmacotherapy of Psychotic Depression (STOP-PD) and summarizes research on the epidemiology, significance, diagnostic complexity, and treatment of psychotic depression. Case vignettes are provided to highlight diagnostic and therapeutic issues. (Additional information on the STOP-PD project is available from Meyers and Avari.)

A brief overview

Conceptualization of psychotic depression as a distinct variant of major depression is a recent development in psychiatric nosology that largely results from advances in psychopharmacology. Although the occurrence of delusions in a subset of patients with a severe depressive illness was described by Kraepelin in the early 20th century, the impact of associated psychotic phenomena on treatment response and prognosis was not recognized until the introduction of antidepressants more than a half century later.

Early placebo-controlled studies using TCAs demonstrated that patients with major depression associated with delusions had very poor treatment responses. These findings focused attention on whether delusional depression is a distinct subtype of major depression. In 1977, Glassman and colleagues reported that 95% of 25 hospitalized patients with melancholic nondelusional depression treated with higher than median imipramine dosages achieved remission. Only one-third of the subgroup of control patients with delusions achieved remission.

These results stimulated research into the clinical characteristics, treatment response, and prognosis of psychotic major depression (PMD). These studies led to a shift from DSM-II conceptualization of affective psychosis as largely a function of severity to the inclusion in DSM-III of major depression with psychotic features as a diagnostic subtype that requires delusions and/or hallucinations in association with major depression. In DSM-5, the presence of psychotic features is a specifier

and not indicative of a subtype, because the presence of psychotic features does not preclude the presence of other specifiers, such as melancholia.

The overall community prevalence of PMD is 0.4%; it occurs in 14% to 20% of individuals with MDD. The prevalence of PMD is markedly higher among hospitalized patients; it exceeds 25% in mixed-age adults and occurs in up to 45% of depressed geriatric inpatients.

PMD is associated with severe health consequences. Relapse and recurrence rates approximating 50% have been reported.Compared with patients who have MDD, patients with PMD have poorer outcomes; they have more residual symptoms, greater functional impairment, and more frequent suicide attempts as well as more malignant health outcomes.

An index episode of PMD predicts a greater than 2-fold higher 15-year mortality rate and 3-fold greater risk of suicide after an initial suicide attempt. The longitudinal risk for suicide is substantial because approximately 20% of patients with PMD make a suicide attempt during an episode. The association between suicidal outcomes and PMD presumably results from the behavioral impact of PMD: conviction about highly pessimistic and/or paranoid beliefs that occur in association with the pain of depression may make the choice of suicide appear as rational. Therefore, depressed patients must be assessed for both suicidal and delusional ideas, and depressive and psychotic domains of illness must be treated.

Diagnosis

PMD is often considered interchangeable with delusional depression because the vast majority of patients with psychosis have delusional ideation, whereas hallucinations without delusions are less common. Delusions are fixed beliefs that are resistant to the laws of logic and evidence to the contrary. Psychiatrists expect their depressed patients to have pessimistic and fearful concerns; unfortunately, extra diagnostic rigor is required to differentiate depressive ruminations from the fixed beliefs of PMD.

In STOP-PD, 27% of patients who had delusions did not receive a diagnosis of PMD. Because depressive ruminations that focus on themes of somatic, financial, and guilty concerns are expected concomitants of MDD, clinicians may ignore the question of whether these concerns are held fixedly and are influencing the patient's behavior. Paranoid concerns are more likely to focus attention on the possible presence of delusions, particularly if the fears are not congruent with a depressive theme.

In light of diagnostic inaccuracy, it is not surprising that nearly 20% of research participants who met criteria for PMD had not received antidepressants before study entry, 25% had not received an antipsychotic medication, and only 10% had received intensive pharmacotherapy with both an antipsychotic and an antidepressant.

An association between an index episode of unipolar PMD and the subsequent development of bipolar disorder has been established. Conversion rates from an index PMD to bipolar disorder as high as 20% and 37% have been reported in clinical samples, particularly if the initial episode occurs in young adulthood or adolescence. In contrast, 10-year longitudinal studies have demonstrated that bipolar disorder developed in only 10.2% to 13.8% of patients who initially had uni-polar PMD.

A recent population registry-based study demonstrated that earlier age of onset and recurrent depressive episodes of unipolar PMD significantly increased the likelihood of conversion to a bipolar diagnosis. Although specific clinical features, such as greater psychomotor disturbance and reverse vegetative signs, are often considered indicative of a bipolar diagnosis, systematic investigations of whether clinical features reliably distinguish unipolar from bipolar depression are lacking.

The following case vignettes highlight the importance of early recognition and effective management.

CASE VIGNETTE

Mrs Burns is a recently widowed 72-year-old. She is admitted to a psychiatric hospital after referral from her internist because of symptoms of sadness, anhedonia, diminished energy, and poor appetite. She acknowledges feeling sad and hopeless but attributes these feelings to her poor appetite, lack of energy, and weight loss. She expresses concern that she is suffering from an undiagnosed cancer, stating that she has no other reason to be depressed.

In the past few weeks, Mrs Burns has seen 3 gastroenterologists and received multiple imaging studies that she felt had missed the malignancy. She does not believe her physicians had deceived her but expresses a lack of confidence in the diagnostic procedures, citing news reports of cases of missed diagnoses. She denies suicidal thoughts or wishes.

The diagnosis is major depression with somatic anxiety and ruminations. Mrs Burns's physical examination and laboratory workup do not show an active medical illness. She is informed that she is suffering from depression and that loss of appetite and weight loss occur commonly with depression. She is treated with sertraline, 100 mg/d, and her mood brightens. She becomes more engaged in activities during the 2 weeks of treatment while she is hospitalized, and she acknowledges that her depression is "50% better."

Although her appetite improves with a small increase in weight, she continues to doubt her psychiatrist's view that her physical symptoms were a result of the depression, and she requests additional GI consultations. In addition, she complains of mild symptoms of nausea and constipation that are considered adverse effects of the medication.

Mrs Burns is discharged as moderately improved, and she agrees to continue the sertraline despite the mild GI symptoms. She is referred to a psychiatrist in her community, and her daughters agree to monitor her adherence to further treatment. Shortly after discharge, Mrs Burns makes a consultation appointment with a new gastroenterologist, specifically requesting a workup for an occult malignancy. After a physical examination and record review, the gastroenterologist informs her that further testing is not necessary and suggests that she discuss her concerns with her psychiatrist. Soon after returning home from this visit, Mrs Burns writes a note expressing her hopelessness, frustration with doctors, and fear of dying in pain. She states that she prefers suicide to a slow, painful death from cancer and takes an overdose of over-the-counter medications.

It is likely that Mrs Burns suffered from an undiagnosed PMD. Neither her somatic preoccupation nor her suicidal risk had been sufficiently assessed during the hospitalization. The chart did not document whether somatic concern had been considered as possibly irrational or whether adding an antipsychotic medication to her treatment had been considered. Although improvement in her depressive syndrome had been easily achieved, reassurance by her psychiatrist had been only transiently and mildly effective.

Mrs Burns had been discharged though her pessimistic preoccupation persisted. The question of whether Mrs Burns required additional treatment for a delusion component of her depression was not addressed and a comprehensive as-sessment of her risk for suicide had not been discussed with her or her daughters. The treatment team expected that Mrs Burns would fully recover from her depression.

CASE VIGNETTE

Mr Harris, a 65-year-old married accountant, is referred for psychiatric treatment before submitting his annual tax return because of depressed mood, anhedonia, anorexia, weight loss, and guilty ruminations about having submitted inaccurate tax returns in previous years. Mr Harris shamefully acknowledges that he had exaggerated a tax deduction by $500 on his last return, and he now believes that he will be audited and arrested for tax evasion. He voices concerns that the FBI is investigating him and that both his and his family's reputations would be ruined as a result. He denies having suicidal ideation or intent.

His family reports that he has been scrupulous in his business affairs and in preparing his tax returns. They are convinced that his worry about an excessive deduction is irrational. Despite the family's reassurance, Mr Harris has retained an attorney.

Mr Harris's psychiatric diagnosis is major depression, and he receives an antidepressant and a low-dose antipsychotic. His family agrees to monitor and otherwise support Mr Harris's treatment. After 3 weeks of treatment, Mr Harris's mood, appetite, and interest in social activities improve. At the psychiatrist's

recommendation and with Mr Harris's consent, an accountant is retained to prepare his new tax return and communicate with the IRS about paying any fine due for his past exaggeration of a deduction. Nevertheless, Mr Harris continues to express concern that he is being investigated and that he will be sent to prison for his past tax report error.

The day after his new tax return is submitted, Mr Harris reads a news article about the arrest of a public figure for tax fraud. He writes a letter to his family apologizing for his past behavior and stating that he wishes to spare them humiliating consequences of his behavior. He hangs himself.

Mr Harris's major depression was associated with a distressing irrational idea that led him to retain an attorney. Despite being an accountant, he had grievously exaggerated the impact his alleged past error would have on his and his family's future. Although Mr Harris's overall mood improved with an antidepressant and a low dose of an antipsychotic, his preoccupation with a mood-congruent delusion of deserved punishment persisted. The dose of antipsychotic or the specific medication may have been inadequate, or Mr Harris may have been resistant to pharmacotherapy.

His psychiatrist had recognized the seriousness of Mr Harris's delusion and implemented interventions designed to reassure him. However, Mr Harris's delusion was irrational and was impervious to both reassurance and the realistic step of having his accountant submit a new tax return. Most important, Mr Harris's suicidal risk was not systematically assessed and the option of treating his acute episode in a hospital was not explored.

In retrospect, the intensity of Mr Harris's preoccupation with his delusion and the expected consequences to him and his family if the belief were valid should have led to a deliberate consideration of hospitalization. An imminent risk of suicide should guide the decision about outpatient versus hospital treatment of PMD. More aggressive combination pharmacotherapy or electroconvulsive therapy (ECT) would have been more easily rendered on an inpatient basis, and the tragic outcome may have been avoidable.

Acute and postremission treatment of PMD

Consensus guidelines consider 2 treatments as effective for PMD: ECT and pharmacotherapy that combines an antidepressant with an antipsychotic. Results from a STOP-PD randomized controlled trial (RCT) demonstrated the efficacy of combined olanzapine (average dosage, 14.7 mg/d) and sertraline (average dosage, 170 mg/d) compared with olanzapine plus placebo.[10]The 12-week remission rate of 41.2% was comparable to remission rates reported in RCTs of less depressed outpatients.

A recent RCT using quetiapine (average dosage, 600 mg/d) combined with venlafaxine (average dosage, 375 mg/d) demonstrated efficacy comparable to that

found in STOP–PD, with a 41.5% remission rate. The STOP-PD results underscore the importance of deciding on postremission treatment: STOP-PD participants experienced significant weight gain and increases in their plasma lipid levels during the trial. Therefore, the risk to benefit ratio of continuing combined treatment versus discontinuing the antipsychotic following a sustained remission of PMD has great clinical importance. The ongoing STOP-PD II trial, Sustaining Remission of Psychotic Depression, investigates this question by randomizing patients with symptom remission to continue sertraline plus olanzapine or to continue sertraline plus placebo for 36 weeks.

Future directions

Knowledge about the diagnosis and treatment of PMD has increased markedly over the past 35 years. Nevertheless, advances in the understanding of underlying pathophysiology of one of the few spontaneously occurring and fully reversible psychotic conditions have emerged slowly. The cortisol dysregulation hypothesis continues to gain support, with an increasing focus on genes that regulate central glucocorticoid receptors. From the perspective of phenomenology, conceptualization of psychosis and delusional thinking as domains of interest would facilitate research into irrational thinking within and across psychiatric disorders.

Psychotic thinking would be a more focused domain than positive symptoms for inclusion in the NIMH Research Domain Criteria (RDoC) project. Irrational thought processing meets the RDoC project criteria of both being a dimensional pathology and occurring across multiple psychiatric diagnoses. Including irrational thinking as a specific domain would facilitate research into the underlying neuro-biological and neuropsychological mechanisms of delusional thinking and further our ability to characterize and treat this important area of psychopathology.

Acknowledgment—STOP-PD researchers include Alastair Flint at the University of Toronto, Anthony Rothschild at the University of Massachusetts Medical School, Ellen Whyte at the University of Pittsburgh School of Medicine, Benoit Mulsant at the Centre for Addiction and Mental Health in Toronto, and Barnett Meyers at Weill Cornell Medical College. The NIMH has supported the STOP-PD studies of unipolar major psychotic depression for more than a decade (MH 62446, MH 62518, MH 62565, and MH62624).

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Dr Meyers is Professor of Psychiatry at Weill Cornell Medical Center in White Plains, NY. He reports that he has received grant support from Pfizer for an NIMH research study.

A Rational Suicide? Case Consultation and Quiz Commentary

Psychiatric Times
Cynthia Geppert, MD, MA, PhD, MPH, MSBE, DPS, FAPM
July 27, 2015 | Suicide
By Cynthia Geppert, MD, MA, PhD, MPH, MSBE, DPS, FAPM
The author offers a brief commentary in response to feedback from readers of a previously published case.
The thought of suicide is a great consolation: by means of it one gets successfully through many a bad night.
—Friedrich Nietzsche, Beyond Good and Evil
In the article "A Rational Suicide?" readers were asked to imagine that they were the clinical ethics consultant (CEC) called to the emergency department (ED) to deal with the distressing dilemma summarized below. They were then presented with 4 key questions—each of which is examined in this analysis. Readers were also invited to post their comments.
Here I offer a brief commentary in response to the many moving and thoughtful Internet postings received from readers of the case.
Case summary
Mrs N is a 65-year-old retired nurse who, driven by seemingly intractable nausea and vomiting, decides to kill herself with an overdose of fentanyl she has stockpiled. She informs her ex-husband, who is also her power of attorney (POA), of her plans and asks that once she is dead he come to her house and take care of her affairs. Unfortunately, her ex-husband arrives while she is still alive and calls 911. When brought to the ED, Mrs N refuses all medical intervention and both she and her ex-husband angrily plead with staff to allow her to die, leading the staff to request an emergency ethics consultation.
Analysis
Question 1: The ED nurse asks if she has a legal and ethical duty to report the ex-husband to law enforcement because he knew his ex-wife intended to commit suicide and took no steps to prevent this. As the ethics consultant, how would you respond?
In a passive and permissive role, the ex-husband allowed the suicide attempt, but he took no active role, such as obtaining or administering the opioids to assist his ex-wife to kill herself. Since there is no real direct "aiding and abetting" of the suicide attempt, it is not probable—although given the vagaries of the legal system, not impossible—that the husband would be criminally charged. In a morality rooted in deontology or religion, there would likely be an obligation for any individual to intervene to defend the sacredness of life. Remember that anyone can file a report with the police, and the nurse's claim of conscience that she needs to do so should be respected.
In general, adult protective services do not get involved in cases of elders with intact decision-making capacity. The geriatric consultant's description of Mrs N as being a "completely cognitively intact woman" with "good coping skills" is not likely to attract the attention of overburdened state social services. The final choice is in part already in motion: in most institutions, the CEC works with, or for, the ethics committee. And once Mrs N became an

inpatient, whether medical or psychiatric, the likelihood is high that clinical staff will query the CEC about visiting privileges for the ex-husband.

Question 2: Should the ex-husband be allowed to serve as the POA?

It is easy to envision nursing or social work staff raising the issue of the appropriateness of the ex-husband continuing to serve as POA because it springs from the same well of moral distress as the nurse's belief that she should report the ex-husband at least for complicity. The CEC must first remind all involved, including the ex-husband, that a POA only goes into effect when a patient loses capacity, and in this case, Mrs N was deemed cognitively intact. Mrs N's husband voiced his view that his wife should be allowed to die. Since her husband is the POA but did not prevent his wife from trying to kill herself, the staff believe that at the bare minimum, he should be prohibited from making medical decisions on his ex-wife's behalf—at least until this acute episode resolves.

The devil in the details is "whose best interests?" For Mrs N and the ex-husband who knows her best and cares about her most, the paradoxical truth is that the suicide attempt actualized their shared conception of best interest. Obviously it does not cohere with the ethical schema of most medical professionals in the scenario, although fascinatingly, the majority of readers endorsed this position.

The idea of "best interests" as a standard for decision making is actually in many ways far less objective than it appears, and legal rulings and ethical consensus direct that it only comes into play when a patient's wishes and values are unknown.Research has validated the commonsense intuition that neither decision-making standard is as existentially valid or holistically reliable as the judgment of a trusted surrogate. This leaves us with the burden of proof lying with the health care team to show clear and convincing evidence that because of his inaction, the ex-husband, who is the patient's chosen surrogate, cannot ethically remain as POA.

Question 3: Should the physician honor the patient's request to be DNR?

This was the most controversial question. In most EDs and hospitals, any patient who is being treated for the complications of a suicide attempt is prohibited from being DNR. From a risk management perspective, this makes perfect sense and is the reflexive intuition of most health care professionals.

Ethicists and some clinicians, however, challenge the presumption and argue that if the patient previously expressed (eg, in an advance directive) a preference for DNR as a choice separated in space and time from the suicide attempt, it should be honored. The patient's regaining capacity obviates the need for the POA. However, if she lacked capacity, the same objections examined earlier (that the ex-husband is an unfit POA) as well as that the physician would be an accomplice can again be raised.

Question 4: Once the patient is medically stabilized, which of the following is the most ethically justifiable option if she continues to state her intention to return home to again attempt suicide?

The final question brings the case squarely into the realm of psychiatric diagnosis and treatment. Readers' responses turned on whether they thought suicide and rational are contradictory terms. The majority embraced the last option and believed Mrs N had the right to end her life and that her husband had the responsibility to help her ease her suffering.

In the case of Mrs N, the CEC seeks the expertise of the psychiatric consultant who initially is equally confounded and endorses that the patient does not meet criteria for psychiatric hospitalization, voluntary or involuntary. Fortunately, the two consultants are able to persuade Mrs N to accept admission to the medical unit and to give the medical specialists one more

opportunity to control her symptoms. She is admitted, though making her conditions clear: if no sustained and significant relief is obtained, she will return home to commit suicide.

Response to readers' comments

Psychiatrists have done a profound service in critically examining the meaning of the concept of rational suicide for our profession. I would be very foolish to absolutely deny the possibility that there is no problem of human anguish where suicide would not be the most coherent solution. A question mark follows the title of the article "A Rational Suicide?" to underscore that the primary ethics question the case presents is whether in Mrs N's specific set of contextual features, suicide is rational. The urgency of the circumstances, as it so often is in psychiatry, compels the consultants to make decisions amid the mess of the human condition, often leaving them with haunting loose ends. It is interesting that it was not just readers who identified themselves as mental health professionals, but also relatives of persons who had attempted or completed suicide, who poignantly argued for involuntary hospitalization.

Faced with a woman who has demonstrated the resolve and resourcefulness to take her own life, even without a diagnosable disorder, most psychiatrists would not discharge Mrs N home. Some would even go so far as to not even consider voluntary hospitalization, believing that the respective mental health laws in their jurisdictions give them the authority and the obligation legally and ethically to hospitalize Mrs N. That authority is politically predicated on the regnant social policy that suicide is always an irrational act and that the lack of reason stems from a mental illness even if not immediately discoverable.

Other readers suggested what I think is the wisest course—the one ultimately followed—to respect Mrs N's decision to be admitted to a medical ward with the goal of receiving aggressive treatment of her symptoms in the belief, and yes the hope, that more effective interventions could render Mrs N's life bearable. The psychiatric consultant with the counsel of the CEC does not threaten Mrs N with an ultimatum if such amelioration is not successful. Rather, the psychiatrist takes advantage of the breathing room the hospitalization affords to ponder Ramsey's wise words, to engage "the patient as a person."

Part of that engagement is for the psychiatrist and the CEC to accept— without endorsing—Mrs N's right to determine the conditions of her life and death. The psychiatrist will lose any chance to ever get to know Mrs N's story if he or she does not phenomenologically embrace her self-portrayal as a mentally healthy woman of libertarian philosophical bent. Intellectual sparring or paternalistic insistence on "professional judgment" will only fulfill the prophecy Mrs N has already uttered about the failures of the medical profession to provide a life she feels is livable.

The ethical duty of the psychiatrist and of the CEC is not to unravel the Gordian knot of rational suicide or to change public policy. It is even less to avoid a malpractice suit—although, sadly, more than a few readers and psychiatrists would see this as the over-determining factor in the case. The true duty is articulated in the thinking of my colleague Rebecca W. Brendel, MD, JD:

It is also the role of the psychiatrist to understand the patient's fears, concerns, life goals, and coping style and how these and other factors may be influencing the patient's wish to die. Such an enterprise need not lead to the conclusion that there are not rationally motivated desires to hasten death. But the default position of the psychiatrist, given the obligation of physicians to act in the preservation of life, and the fact that most hastened death in the form of suicide is associated with mental illness, must be to err on the side of caution, life, and safety when evaluating and treating patients who wish to hasten their death.

Intragastric Balloon for Weight Loss

David J. Bjorkman, MD, MSPH (HSA), SM (Epid.) reviewing Gaur S et al. Gastrointest Endosc 2015 Jun.

In a review of one newer balloon, about half of weight loss was sustained 1 year after balloon removal.

Interest is growing in endoscopic approaches to promoting weight loss. New intragastric balloons have been developed since the first balloon was withdrawn almost 3 decades ago. In a systematic review of one newer balloon, the Orbera balloon, investigators summarized the results of 7 studies reporting weight loss at 3 and 6 months and 11 studies reporting sustained weight loss after balloon removal.

Results showed the following:

- The average weight loss was 12.9 kg after 3 months and 16 kg after 6 months.
- Eighty percent of the 6-month weight loss was achieved in the first 3 months.
- An average of 52% of weight loss was sustained 1 year after balloon removal.
- Two cases of intestinal obstruction occurred.
- Balloon leakage was the most common adverse event.
- Data from limited studies suggested that leakage was more common when the balloon was left in place longer than the recommended 6 months.

The authors conclude that newer intragastric balloons present a potential intermediate option between diet and exercise therapy and bariatric surgery.

Introduction: The State of Addiction Psychiatry

Psychiatric Times
Ryan Mals
Bellelizabeth Foster, MD
April 30, 2015 | Special Reports, Addiction , Alcohol Abuse, Gambling, Substance Use Disorder
By Ryan Mals and Bellelizabeth Foster, MD

The articles in this Special Report provide a broad, cross-cutting perspective on the current state of addiction psychiatry, insofar as it may pertain to your own clinical practice.

Over the past 50 years, the addiction field has exploded, thanks to a convergence of neurobiological research, psychopharmacological advances, and an exponentially growing evidence base. Nevertheless, despite a deep-rooted foundation, addiction psychiatry faces an ongoing struggle to achieve acceptance among physicians—from general practitioners to primary care psychiatrists. All too often, true neuro-pathologies such as alcoholism and injection drug use are marginalized, ignored, and sidelined for comorbid medical—or psychiatric—diagnoses.

In 1952, DSM-I formally recognized addiction as a subset of "sociopathic personality disorder" (alongside dyssocial reaction and unspecified sexual deviation). Almost 3 decades later, DSM-III dedicated an entire chapter to substance use disorders, providing separate abuse and dependence criteria for alcohol, barbiturates and sedative/hypnotics, opioids, amphetamines and sympathomimetics, phencyclidine (PCP)/arylcyclohexylamines, hallucinogens, cannabis, and tobacco. DSM-IV famously incorporated polysubstance dependence, which was redacted in DSM-5 to allow better conceptualization of individualized patient care.

In addition to removing polysubstance use, DSM-5 features several salient changes in its approach to patients struggling with addiction. First, addictive disorders no longer exist as "abuse" or "dependence"; both criteria sets have been combined into "use disorders." This change promotes diagnostic reliability, validity, and clarity

while it proposes a unidimensional spectrum of severity informed by both abuse and dependence.

Next, "craving" now serves as a symptom of substance use disorders. This addition reflects recent strong correlations of subjective craving data and functional neuroimaging. Conversely, legal consequences are no longer included as a criterion for substance use disorders; compared with other diagnostic criteria, their diagnostic yield was negligible because of their relatively low prevalence and accuracy.

Several nonsubstance addictive behaviors have been reclassified. Pathological gambling now falls under addictive disorders (previously it was an impulse-control disorder), and addiction to online video games is considered a "condition for further study." Both shifts echo an increasing prevalence and expanding evidence base.

The articles in this Special Report provide a broad, cross-cutting perspective on the current state of addiction psychiatry, insofar as it may pertain to your own clinical practice. We hope you enjoy this addiction "smorgasbord" featuring cannabis use disorder, psychosocial addictions, pathological gambling, opioid use disorder, club drugs, and Internet gaming disorder.

In this Special Report:

Introduction: The State of Addiction Psychiatry

An Update on Street and Club Drugs: What Clinicians Need to Know

Opioid Use Disorder: Update on Diagnosis and Treatment

Marijuana and Madness: Clinical Implications of Increased Availability and Potency

A Brief Review of Gambling Disorder and Five Related Case Vignettes

Video Games: Recreation or Addiction?

The Therapeutic Alliance and Psychosocial Interventions for Successful Treatment of Addiction

Disclosures:

Mr Mals is a fourth-year University of New Mexico medical student, currently awaiting Match results for general psychiatry. Dr Foster is Assistant Professor of Addiction Psychiatry at the University of New Mexico and Medical Director of the Services for Teen Addiction in Recovery in Albuquerque. They report no conflicts of interest concerning the subject matter of this Special Report.

A Brief Review of Gambling Disorder and Five Related Case Vignettes

Psychiatric Times
Iman Parhami, MD, MPH
Timothy Fong, MD
April 30, 2015 | Special Reports , Addiction, Challenging Cases , Comorbidity In Psychiatry, Gambling , Suicide
By Iman Parhami, MD, MPH and Timothy Fong, MD
The loss of control over urges and behaviors may be the central component of gambling disorders, but there is so much more to consider. Individuals with these problems have exponentially higher rates of suicide attempts and completions.
Nearly 4% of the population has gambling-related problems, and 6% will experience harm from gambling during their lifetime—including financial, legal, relational, and health problems. In addition, individuals with gambling problems have exponentially higher rates of suicide attempts and completions. One study found that 81% of pathological gamblers in treatment showed some suicidal ideation, and 30% reported one or more suicide attempts in the preceding 12 months.
DSM-5 criteria for gambling disorder represent the most common symptoms experienced by those with gambling problems. These symptoms characterize 3 heterogeneous dimensions related to gambling disorder: damage or disruption, loss of control, and dependence. The loss of control over urges and behaviors may be the central component of gambling disorders, and the inability to control gambling may be a component of a progressively worsening process in the life span of some gamblers.
Individuals who encounter gambling-related problems but who do not reach the diagnostic threshold (subthreshold gambling disorder meets only 1 to 3 criteria) are referred to as problem gamblers. For the most part, those with subthreshold gambling disorder continue to experience social, psychological, and health repercussions but to a lesser degree. They are also at increased risk for progression to gambling disorder compared with non-gamblers.
Severity
Gambling disorder is referred to as a hidden addiction because of the minimal signs and symptoms associated with this condition. The level of severity can also be concealed and involve multiple components. For example, a gambler who "hits rock bottom" (or one who has lost everything, including financial assets and social relationships) may have stopped gambling because of the lack of finances, but he or she may be severely depressed and suicidal because of the ongoing repercussion. Other components of severity include gambling behavior (frequency, duration, amount gambled), extent of gambling desires (cravings, urges), repercussions (eg, employment, legal, relationships), level of control, and comorbid symptoms (eg, suicidality, impulsivity, depression). These factors help predict treatment outcome and determine the appropriate treatment (ie, brief intervention, intensive outpatient, hospitalization). In research, severity is usually assessed using the total number of criteria endorsed, which can also be a quick and straightforward method in the clinical setting.
Comorbidity
Gambling disorders are strongly associated with comorbid psychopathology. A meta-analysis of 11 population surveys found high mean prevalence for nicotine dependence (60.1%), a substance

use disorder (57.5%), mood disorders (37.9%), and anxiety disorders (37.4%).[1] A longitudinal 3-year study also found that any mood, anxiety, or substance use–related disorder was more likely to develop in individuals with either subthreshold gambling disorder or gambling disorder than in those who did not gamble.

Clinically, it may be helpful to assess sleep. Those with gambling problems have an increased risk of difficulty in initiating sleep, maintaining sleep, and more and early awakenings. Sleep disturbances can impair self-control and decision making, increase impulsivity, degrade cognition in executive functioning tasks, attenuate responses to losses, and increase expectations of gains that can affect gambling behavior.

Treatment

There are no FDA-approved pharmacological treatments for gambling disorder, but several studies have evaluated the effects of medications on gambling behavior and comorbid symptoms. Grant and colleagues reviewed 18 double-blind placebo-controlled studies that included antidepressants, antipsychotics, mood stabilizers, glutamatergic agents, and opioid antagonists. Although the results were mixed and conclusions were limited because of the small sample sizes, opioid antagonists and glutamatergic agents (N-acetylcysteine) seemed to have the most promising results, especially for those with intense gambling urges.

A number of psychosocial strategies have shown promise in controlling aberrant gambling behavior, including self-help manuals, brief one-session interventions (motivational therapy), psychodynamic therapy, cognitive-behavioral therapy (CBT), and referrals to 12-step support groups. Research findings indicate that the treatment for gambling disorder not only reduces gambling behavior but can also help reduce comorbid psychiatric symptoms, such as anxiety and depression; improve quality of life; decrease psychological stress; and decrease the likelihood of comorbid psychopathology.

CASE VIGNETTE 1

Jack, a 16-year-old 10th grader, is brought by his mother for evaluation of his "excessive online gaming." Jack's mother is concerned that her son plays casino-based "freemium" games 5 hours every day. (Freemium games are free to download but require tokens that are purchased with real money and gambled among players.) He buys approximately $30 worth of tokens every day and has spent more than $5000 on tokens in the past 6 months. He constantly argues with his parents regarding his playing time, his school work has deteriorated, and he no longer has any social interactions.

Jack admits that he lies to his parents about the extent of his playing—he sometimes plays more than 10 hours a day. He has a hard time stopping and usually plays until he loses all his tokens. He uses his mother's credit card to buy tokens without permission. He is proud of his online accomplishments and enjoys the winning and competition with real adults. Although he now has no desire to interact with peers outside of school, he had enjoyed participating in a recreational sports league in the past.

Jack does not appear to suffer from any other disorder. He has never had problems with alcohol or drugs, and he has never seen a mental health professional or received psychotropics. His childhood and development have been without incident. Last year, his mother returned to work and Jack started taking care of his 7-year-old sister after school (during which he games the most).

During the initial session, gaming patterns and repercussions are discussed (financial, educational, and developmental). Recommendations are made that include changing passwords to the app store and limiting Internet access to supervised sessions, and Jack's access to his

mother's credit card is cut off. After-school activities for both children are also highly encouraged, possibly restarting recreational sports competitions for Jack. Potential positive reinforcement methods for complying with clean Internet play are also discussed. The family is referred to a family therapist to continue working on family dynamics.

CASE VIGNETTE 2

A 19-year-old college sophomore is referred by student health for evaluation of his gambling problems. Michael's gambling has become pathological in the past year: he either bets on sports online or spends about 6 hours at a local casino daily. Although he does not work, he lost $50,000 in the past year, using money from his sports scholarship and financial aid. His mother has bailed him out multiple times by paying his credit card bills. He still has a credit card debt and owes money to his friends, which totals $25,000. He usually chases his losses, has strong cravings to gamble during the day, and experiences anxiety trying to find money to use for gambling. The time he spends on academics and team practices has become significantly reduced.

His primary care physician (PCP) prescribed stimulants after a diagnosis of ADHD in middle school, which Michael took until 12th grade. He has never seen a mental health professional or taken any psychotropic medication. He started binge drinking at college parties (probably twice a month, enough to black out); in addition, he smokes one blunt of marijuana every week.

Michael started gambling recreationally with friends in middle school, but he acknowledges that his problem controlling gambling started last year. Although he is disheartened by his gambling problem (and its repercussions), he is not depressed, still enjoys hobbies (which he indicates is gambling), and has fun with his girlfriend. He seems intelli-gent and brags about knowing the poker odds. He is seeking treatment because he wants to control his gambling (make only smart bets or play the good hands). His biggest problem is "losing a few bets in a row and going on tilt!"

During the first session, gambling patterns and repercussions are discussed, which he had initially minimized (ie, the possibility of losing his scholarship and being kicked off the team). He agrees to restart treatment with a stimulant, to include his mother in the next session via phone, and to go to Gamblers Anonymous. He agrees to continue CBT at the student health center to work on his aberrant alcohol use.

During the second session (3 weeks later), he reports that he has restarted the stimulant, which helps his impulsivity and studying habits. He has completed 8 sessions of CBT at the student center. He went to a Gamblers Anonymous meeting but did not agree with their tenet for abstinence. His mother agrees to stop bailing him out, control his credit cards and scholarship checks, and provide a limited allowance.

For the next few months, his gambling decreases (both in duration and frequency), but he places larger bets and loses more. Since his mother stopped bailing him out, he borrows money from a loan shark. He is kicked off the team and his scholarship is terminated. He decides to contact a state-funded mental health professional for more regular therapy sessions. He also agrees to ask the loan shark for a repayment plan.

By the fifth session (4 months after his initial presentation), he has stopped gambling and has a part-time job. He is making regular payments to his loan shark, studying more, drinking less alcohol, and playing more sports recreationally. He still enjoys gambling but now is aware of the repercussions. He is more focused on raising his grade point average and returning to the sports team.

CASE VIGNETTE 3

James, a depressed 40-year-old poker player, is referred by his wife. He was laid off from work 8 months earlier. Since then he plays poker for 8 hours a day at a nearby casino. He gambles "out of boredom" and enjoys the social atmosphere. Although he is well-off financially, he has lost more than $200,000 in the past year. He now plays at higher-limit tables and chases his bets. He lies to his wife regarding his gambling and is on the brink of getting a divorce. He started playing poker as a teenager and had weekly poker games with his colleagues at work.

He lacks motivation, has stopped taking care of himself, and has gained 30 pounds in the past year. He has a hard time falling asleep and at times is restless in the mornings. James has had 3 episodes of depression in the past; he has been taking aripiprazole, citalopram, and bupropion (prescribed by his PCP) for the past 6 months. There is no his-tory suggestive of mania, hypomania, suicidality, or aberrant substance use.

During the first session with James and his wife, his recent gambling winnings/losses are reviewed, including bank statements that his wife brings in. He is surprised at the total amount of losses. He loves poker, but he does not want a divorce. He agrees to give all his bank cards to his wife, ban himself from local casinos, and work on saving his marriage. The couple are given a self-help workbook and listings for Gamblers Anonymous and Gam-Anon, and proper sleep hygiene is emphasized. The couple are also referred to the state-funded gambling provider network to receive therapy to work on their relationship.

Mirtazapine is started to help with depression, and aripiprazole is tapered. (Case report findings suggest a potential correlation between aripiprazole and excessive gambling, which is similar to the association between dopamine replacement therapy for Parkinson disease and gambling.9)

By the next session, James has stopped gambling because he no longer has easy access to money. He has also started attending Gamblers Anonymous several times a week and enjoys their camaraderie. He appreciates how attending Gamblers Anonymous has helped diminish his strong urges to play poker.

By the fourth session (third month), he has completed his résumé and started exercising again. His sleep is improved, he regularly attends meetings of Gamblers Anonymous, and he has a sponsor in addition to making a commitment to the group. He is also in the process of completing 12 sessions with the marriage and family therapist. He misses playing poker, but realizes how abstaining has improved his relation-ship with his wife.

CASE VIGNETTE 4

Jackie, a 34-year-old nurse, is referred by her coworker for gambling at work. Compelled by her colleague, Jackie came to the addiction clinic to receive help for her uncontrollable need to gamble at work. She plays online slots on her phone for about 6 hours during her night shifts; after work, she usually tries to win back her losses at the local casino. Although she has lost $50,000 in the past 6 months, with an annual salary of $150,000, she does not have any financial difficulties and is still well regarded at work.

Six months earlier, Jackie called off her wedding after discovering her fiancé's infidelity. Since that time, gambling has been a great escape for her, specifically helping with ruminations. She is sad, has almost daily crying spells, lacks motivation to care for herself, has problems falling asleep and sustaining sleep, and has some thoughts that she may be better off dead. She is also irritable, easily snapping at colleagues and difficult patients at work. She drinks several glasses of wine every day to "help her nerves."

Jackie describes some history suggestive of hypomania (not sleeping for a few days, very energetic, happy, impulsively shopping, gambling, and having sex). She carries diagnoses of bipolar disorder, depression, borderline personality disorder, and ADHD. When she was 17, she

had a psychiatric hospitalization after breaking up with her boyfriend; she had suicidal ideations and self-injurious behavior (cutting). Jackie saw a therapist for 3 years, went to an accelerated nursing school, and currently works full-time at the hospital. She sees a psychiatrist (about twice a year), who prescribes quetiapine extended-release. Her PCP also prescribes trazodone, fluoxetine, methylphenidate (twice daily), clonazepam (3 times daily), and zolpidem.

During the first session, Jackie is ambivalent about treatment for her gambling, but she does want help for her insomnia, irritability, and anxiety. She agrees to consolidate her prescriptions to one prescriber to optimize medications. She receives psychoeducation regarding the importance of sleep hygiene, especially the effects of smoking, alcohol, stimulants, and shift work. The repercussions of her gambling are also discussed, and she is given a self-help workbook with listings for Gamblers Anonymous meetings. She agrees to taper off most of her medications and to start lamotrigine.

During the second session (10 days later), she reports that her gambling at work has decreased significantly because she was being monitored by her colleagues, but her gambling outside of work has increased. She also started melatonin and diphenhydramine on her own to help with insomnia. Her passive suicidal ideations are stronger, because she thinks that she is not doing anything productive with her life. She does not have a specific plan to hurt herself; she believes that suicide is immoral; and she does not want to voluntarily admit herself to an intensive outpatient program, a residential treatment program, or an inpatient unit.

Jackie continues to be irritable and to have poor self-care and low self-esteem. She enjoys talking during the session and wants to come more often. She has not been to any Gamblers Anonymous meetings because she does not believe that she has a gambling problem. Medications continue to be optimized, and the benefits of sleep hygiene are reinforced. She is also referred to a state-funded therapist to help with her gambling problems.

During her third and fourth sessions (weekly), she reports that the new medication regimen is finally working and she feels less irritable. She has not gambled at work during the past week and feels good, and she has started working more shifts (about 90 hours per week). Consequently, she is usually exhausted af-ter work and does not have the energy to go gambling.

At the seventh session (about 10 weeks after intake), Jackie reports that her work shifts have become more irregular. She works subsequent day and night shifts, and then has a few days off. During her most recent off days, she accepted an invitation for free accommodations and a spa package at a casino/hotel. In those 3 days, she lost $30,000 and gambled for 40 hours. She maxed out her credit cards and emptied her savings account. She finally agrees that she has a gambling problem. She plans to remove herself from the casino's mailing list, ban herself from the local casinos, close her online casino gambling accounts, schedule an appointment with the state-funded therapist, and ask her brother to start controlling her finances.

During the next 6 months (about 15 sessions), she stops gambling. She completes 10 sessions of gambling treatment with the state therapist and decides to continue the therapy out-of-pocket. Her sleep has improved, and her irritability and anxiety have decreased. Jackie also has started working only regular day shifts and has started exercising and socializing with old friends.

CASE VIGNETTE 5

Mrs Kim, a 60-year-old manic gambler, is brought to the emergency department by her daughter for bizarre behavior. For the past month, Mrs Kim has been gambling more than usual and today she returned from the casino after gambling for 48 continuous hours. She had maxed out her credit cards and emptied her savings account. A family friend saw her at the casino acting provocatively toward random strangers. Apparently, she has not slept for the past 3 days. Her family has never seen her act this way.

Mrs Kim has no psychiatric history other than complaining of boredom and lack of motivation to her PCP last month, who prescribed an antidepressant.

Gambling has been a significant part of her life for years; she has been going to the local casino at least once a week for the past 16 years and playing for 5 to 8 hours each time. Before this past incident, she has never gambled more money than she could afford or chased her bets. She has also never experienced gambling-related repercussions.

On evaluation, Mrs Kim is restless but alert and oriented. She is talkative with rapid speech. She reports that she feels "amazing"; her affect is labile—she cries when discussing her deceased husband and then suddenly starts making jokes. She is fixated on leaving the hospital and returning to Thailand to see her deceased mother (whom she believes is still alive).

She is admitted to the inpatient unit after a negative medical workup. Medication-induced bipolar and related disorder are suspected. Her antidepressant is discontinued and a low-dose antipsychotic is started. Fourteen days later, she is discharged: her delusions and manic symptoms have resolved, including her urges to gamble uncontrollably.

Conclusion

These fictional case vignettes represent samples of individuals with gambling problems that any practicing psychiatrist may encounter. Although each patient suffered gambling-related problems, treatments were unique and personalized. It is also not uncommon to include significant others to help control finances, professionals (eg, accountants, lawyers), and health care workers (eg, counselors, therapists) in treatment plans. Specifically, free resources are available and can be used as part of the treatment plan, including self-help manuals and referrals to state-funded provider treatments and 12-step support groups.

Disclosures:

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Opioid Use Disorder: Update on Diagnosis and Treatment

Psychiatric Times
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By Christina Brezing, MD and Adam Bisaga, MD
While opioid dependence is among the most severe and lethal of addictions, it also has the most effective medication treatments. The authors provide 2 case vignettes and a step-by-step process for clinical decision making.
Over the past 10 years, the prevalence of heroin and prescription opioid misuse has significantly increased, in large part because of the increased prescribing of opioid analgesics in the US. As a result, there has been an unparalleled rise in the number of people affected with opioid use disorders and great concerns about the associated morbidity and mortality—including opioid-related overdoses and deaths in conjunction with the spread of infectious diseases, such as HIV infection and hepatitis C.
In this environment, it is imperative that physicians, particularly psychiatrists, are able to identify opioid use disorders; provide education and strategies for harm reduction; and offer effective, evidence-based treatments.
In this brief overview, we provide a step-by-step process for clinical decision making with 2 common-scenario case vignettes.
CASE VIGNETTE
Mr Gordon is a 45-year-old construction worker who had been injured a year earlier when picking up a heavy piece of equipment. His primary care physician (PCP) prescribed oxycodone for the pain. After 3 months, the original dose prescribed no longer controlled his pain, and Mr Gordon began gradually increasing the dose and subsequently running out of his medication earlier than anticipated. After multiple discussions about his increasing use of oxycodone and his failed attempts to cut down on his use, Mr Gordon's PCP stopped prescribing the medication.
After using the last dose of oxycodone, Mr Gordon woke up sweating profusely, with diarrhea, nausea, bone aches and pains, and anxiety. The next morning, he experienced very strong urges to use oxycodone, and he made 3 appointments with different physicians and managed to obtain prescriptions from each of them. In addition, he began buying "blue roxies" (colloquial term for oxycodone 30-mg tablets) from a neighbor, and learned to crush and use 5 to 8 tablets intranasally daily, noting a faster onset of effect.
In a short time, Mr Gordon found himself frequently calling in sick to work so he could continue using the pain-killers. He felt sick on the mornings when he did not have enough pills. He also became depressed and uninterested in socializing, and he had poor appetite and no sex drive. He stopped going to the gym, which had previously been his passion.
After missing work for the third time in a week, he was fired. Out of work and with only a few tablets of oxycodone left, Mr Gordon feels that his use of oxycodone is out of control and that he has become "a different person."
Mr Gordon's diagnosis

In DSM-5, opioid use disorders, like all substance use disorders, have been redefined as a spectrum of pathology and impairment. The criteria for an opioid use disorder are generally the same as in DSM-IV. The diagnostic criteria for DSM-IV abuse and dependence were combined in DSM-5 except for 2 changes: (1) the criterion for recurrent legal problems has been removed and (2) a new criterion for craving, or a strong desire or urge, to use opioids has been added.

In DSM-5, the two disorders of opioid abuse and opioid dependence are replaced by a category of opioid use disorder. A patient must meet at least 2 diagnostic criteria to qualify as having an opioid use disorder. Severity is characterized as "mild" if 2 or 3 criteria are met, "moderate" if 4 or 5 criteria are met, and "severe" if 6 or more criteria are met.

Mr Gordon meets 7 criteria, which qualifies him for a severe opioid use disorder. He demonstrates tolerance to oxycodone; is using more and for longer than intended; has had multiple failed attempts to decrease his use, withdrawal, and craving; has increased time spent obtaining opioids; and has failed to fulfill work obligations.

Mr Gordon also meets criteria for a DSM-5 category of opioid-induced depressive disorder. For that diagnosis, the onset of depressive disorder needs to be temporally connected with the substance use (ie, within 1 month as opposed to before the initiation of substance use or during a prolonged period of abstinence). Moreover, the opioids need to be capable of producing the specific syndrome, which is certainly the case with the depressive disorder.

"While opioid dependence is among the most severe and lethal of addictions, it also has the most effective medication treatments."

Treatment options

In the US, there are 3 FDA-approved medication treatments for opioid use disorders, all of which engage the μ-opioid receptor: methadone, a full agonist; buprenorphine, a partial agonist; and naltrexone, an antagonist. compares the different properties of each medication. While methadone is an effective pharmacological option, because of federal regulations, it is only available at designated methadone administration sites (methadone maintenance treatment programs) and is not available for the treatment of opioid use disorders by prescription.

Patients who desire office-based treatment for opioid use disorders have the 2 remaining options: buprenorphine and naltrexone. When selecting which medication is best suited for your patient, there are several factors to consider, includ-ing clinical history, treatment preferences, available support system, and access to resources. Each of these pharmacotherapies has a potential to decrease or eliminate craving for heroin or a prescription opioid, which helps the patient engage and benefit from a behavioral, abstinence-oriented treatment to achieve recovery—a voluntarily maintained lifestyle characterized by sobriety with care for personal health and relationships.

Buprenorphine partially activates the μ-opioid receptor, at approximately 50% the maximum effect produced by an agonist. At lower doses (16 mg or less), its agonist effect is directly correlated with the dose; however, at higher doses (more than 16 mg), its pharmacological and clinical effects decrease and plateau, with the increasing dose reaching a ceiling above which no further agonist effect is possible. The agonist effects of buprenorphine prevent opioid withdrawal and reduce or eliminate the craving for opioids. In addition to its agonist properties, bupre-norphine has a higher affinity for the μ-opioid receptor than commonly used opioids. As a result, buprenorphine functionally acts as an antagonist, preventing other opioids from binding to the receptor.

Buprenorphine is available in 2 sublingual formulations—as pure buprenorphine (Subutex) and as a buprenorphine/naloxone combination (Suboxone, Zubsolv)—and in a buccal film formulation (Bunavail).

Naloxone is a short-acting opioid antagonist, which is mostly inactive by the sublingual route. The addition of naloxone to the formulation is designed to deter misuse of the medication, since naloxone becomes active and exerts antagonist effects when used intravenously.

Physicians who are interested in using buprenorphine to treat patients with opioid use disorders can obtain a DATA 2000 (Drug Addiction Treatment Act of 2000) waiver by completing training and submitting their waiver of intent as outlined by the Substance Abuse and Mental Health Services Administration (SAMHSA). Training can be completed in person or online (pcssmat.org). The Drug Enforcement Administration will subsequently provide the physician with a separate license number (X-number) to be used when writing buprenorphine prescriptions.

Naltrexone binds to the μ-opioid receptor with a high affinity but does not exert any activity; rather, it prevents binding of agonists or displaces agonists at the receptor. Naltrexone can be administered after detoxification to prevent relapse, when it provides a complete blockade of opioid effects.

Naltrexone is available in an oral tablet formulation that requires daily administration or a once-monthly, long-acting intramuscular injection (Vivitrol) to bypass the difficulties with adherence to daily medication that many patients have at treatment outset. No additional training or licensure is required to prescribe naltrexone for opioid use disorders, but training materials are available (pcssmat.org).

All 3 of these medications should be considered in Mr Gordon's treatment.

Treatment course

After the benefits and limitations of different medication options are explained to Mr Gordon, a decision is made for outpatient buprenorphine induction and maintenance treatment. This choice of treatment is made on the basis of his unwillingness to go through the detoxification and his preference for office-based treatment.

During the first month of treatment, he is maintained on buprenorphine 12 mg/d: he has no cravings and maintains abstinence from opioids as confirmed with weekly urine drug screens. After 2 months of treatment, he requests a dose decrease and the medication is gradually tapered to 4 mg/d. After 1 month of stabilization with buprenorphine, he reports that his depressed mood is resolved, his appetite is improved, and he is going to the gym daily. He is hired by another construction company; he goes to work every day, reengages with his friends, and resumes dating.

He feels that he is "cured" and decides to stop coming to treatment; he self-tapers off buprenorphine and notes minimal withdrawal symptoms. After about 6 months, he begins to casually use oxycodone again because he thinks that he is now able to control use, which he does in the first few weeks. However, his use gradually escalates and after 2 months of using, he admits that he needs help and reengages in treatment.

Given that he had an excellent response with buprenorphine, treatment is re-induced at a dosage of 8 mg/d, which, over 2 to 3 months, is gradually tapered to 4 mg/d. At this point, he has been stable and in recovery from opioids for 3 years. He plans to continue on buprenorphine maintenance indefinitely. He has no mood problems and is very happy with his current health and life situation.

Mr Gordon's case highlights the chronic and potentially exacerbating nature of opioid use disorders, which is similar to other chronic psychiatric disorders, such as bipolar disorder. A long-term focus on medication adherence is needed as well as regular office visits to monitor stability, work on relapse prevention strategies, recognizing destabilizing events, and developing other health-promoting activities.

CASE VIGNETTE

Ms Derbin is a 26-year-old bartender who self-presents for outpatient treatment after injecting heroin for the past month. She first used nonprescribed oxycodone at age 19, when someone introduced her to snorting it at a party. Initially, she used it 1 or 2 times a week, usually on weekends; but over the next 2 years, her use progressed to daily snorting. She is no longer experiencing euphoria with use and is now using primarily to avoid withdrawal symptoms.

When oxycodone became increasingly more difficult to obtain, a boyfriend introduced her to injecting heroin to reduce daily expense and to have greater and faster euphoric effects. In addition to using opioids, Ms Derbin has been a daily marijuana smoker for 10 years and regularly uses intranasal cocaine (14 of the past 30 days), alcohol (weekend binge drinking), and benzodiazepines (mainly alprazolam for 5 of the past 30 days). She also reports a history of ADHD, for which she took stimulant medication from age 13 through 19.

She reports that this is not her first time coming to treatment for opioid use. At age 22, she had an inpatient methadone-assisted detox from opioids; treatment was tapered and discontinued before discharge. She remembers "not feeling well" following her discharge and relapsing 2 days after leaving the facility.

She went to her second detox 6 months later, and this time was discharged to a residential treatment center that followed a therapeutic community model. She stayed there for 3 months and was instructed to "become personally responsible for her behavior to be drug-free." Medication-assisted treatment was not offered, but she was instructed to seek out Alcoholics Anonymous to maintain sobriety.

After her discharge and a total of 6 months abstaining from opioids, she relapsed with oxycodone and benzodiazepines—she notes that she felt "bored" at work and was seeking excitement. She overdosed during the first week, and a friend called an ambulance after she became nonresponsive.

This overdose prompted Ms Derbin to seek treatment again—this time as an outpatient with buprenorphine induction and maintenance. She did well for 2 months while taking buprenorphine, using heroin only occasionally, but she continued to use cocaine and alprazolam. Eventually she began diverting the buprenorphine and attempting to inject it. After 1 month, she stopped injecting buprenorphine and resumed daily injections of heroin. She presents to you with concerns about her injection use. She wants to be detoxified because she does not want to be "dependent on any substance ever again."

History informs treatment considerations

Ms Derbin's previous experience with multiple and varied treatment settings is quite common for many patients struggling with opioid use disorders. Her first two experiences of detoxification without the offer of medication-assisted treatment to prevent relapse is still the most frequently used strategy. However, as demonstrated in this case, patients whose detoxification is not followed by relapse-prevention treatment are at high risk for relapse. As many as 90% of such patients relapse, usually in 1 to 2 months, and unfortunately many will overdose given that they no longer have physiological tolerance to opioids once detoxified.

Detoxified individuals are at greater risk for overdose than those who avoid treatment and continue to use opioids regularly. Individuals who use opioids in the context of sedative and alcohol use are at the highest risk for respiratory suppression and overdose. All opioid users, especially those who decline further treatment following detoxification, should be counseled about the high risk of overdose with relapse and provided with a naloxone rescue kit. Their friends and family need to be educated about how to obtain a rescue kit (SAMHSA Opioid

Overdose Toolkit; projectlazarus.org) and about how to administer the naloxone in the event of an overdose. Patients who inject opioids should also be informed about clean needle exchanges.

Ms Derbin's history indicates a past trial of buprenorphine maintenance with a poor treatment response. While many patients do well with agonist or partial agonist maintenance treatment for opioid use disorder, others do not respond and continue to have cravings and illicit opioid use. Others, such as those engaged in recovery in the 12-step community, find it difficult to accept the idea of being "dependent" on another type of drug/opioid. Given Ms Derbin's personal preference and interest, a trial of antagonist treatment with naltrexone in conjunction with relapse-prevention therapy and psychosocial interventions was agreed on, and her parents were brought in to be a part of treatment.

Transitioning to antagonist treatment

To transition to antagonist treatment, the patient must first go through detoxification. One of 3 detox strategies can be used: agonist-assisted detoxification, symptomatic treatment only with non-opioid medication, or antagonist-assisted detoxification with symptomatic treatment. The main difference between agonist-assisted detoxification and the other two strategies is that withdrawal symptoms tend to be more severe toward the later part of treatment with agonists, while withdrawal symptoms are more severe earlier in treatment with the other two methods. Also, agonist detoxification requires a 7- to 10-day washout period before administration of naltrexone to prevent precipitated withdrawal. Because of this prolonged detoxification period and delay in starting naltrexone, some patients may drop out of treatment and relapse.

Once a patient completes detoxification, a urine drug screen should be obtained to confirm abstinence from all opioids (including buprenorphine). Administering naltrexone to a patient who is still physically dependent on opioids will precipitate a severe withdrawal reaction. If long-acting injectable naltrexone is selected, a trial of oral naltrexone may be given first to ensure that the patient tolerates the medication and withdrawal is not precipitated. If the patient has been abstinent (eg, in residential treatment), naltrexone injection can be given at treatment outset. Monthly injection of a long-acting intramuscular naltrexone is generally preferable to a daily oral administration, especially at treatment outset, because rates of treatment response tend to be twice as high with the long-acting prepa-ration (for more information, see pcssmat.org or SAMHSA'sClinical Use of Extended-Release Injectable Naltrexone in the Treatment of Opioid Use Disorders: A Brief Guide).

Often the psychiatrist is the only health care professional who has regular contact with a patient who has an opioid use disorder. This should be seen as an opportunity to provide prevention strategies, screening, counseling, and possible referrals for co-occurring medical problems commonly seen in this patient population. Given Ms Derbin's recent injection drug use, HIV and hepatitis C and B status should be obtained with routine blood work in addition to referral for hepatitis B vaccinations if she has not already received them.

Ms Derbin's treatment course

Ms Derbin was successfully detoxified with small ascending doses of oral naltrexone and supportive medications, including clonidine, zolpidem, and clonazepam. Subsequently, monthly injections of a long-acting intramuscular naltrexone were started. Her parents were instrumental early in treatment in reminding her of and bringing her to appointments and arranging for her to meet with a physician to better understand the nature of her condition and the role that medication plays in recovery.

As she became more engaged in the relapse-prevention behavioral therapy over time, she lost cravings for the drugs and now only uses marijuana with decreased frequency (from daily use

down to 4 times a week). She has been abstinent from opioids for 18 months with ongoing monthly injections of naltrexone. At present, Ms Derbin reports much greater stability than with previous treatment attempts. When she started working, her PCP prescribed extended-release stimulants to treat symptoms of her ADHD. Ms Derbin reports improvement in work and life satisfaction. She broke up with the heroin-using boyfriend and began attending regular Narcotics Anonymous meetings, at which she has found a community of people she identifies with in recovery.

Conclusions

Many advances have been made in the treatment of opioid use disorders over the past decade. While opioid dependence is among the most severe and lethal of addictions, it also has the most effective medication treatments. Treatment is the most important strategy to reduce death due to opioid overdose—pharmacological treatments reduce the risk by 90%. The challenge now comes with implementing medication-assisted treatment into a widespread community practice to allow easier access to evidence-based care for patients. The medication-free approach cannot be justified as the only treatment for opioid addiction: overwhelming evidence exists to support the greater success of a medication-assisted approach.

Psychiatrists are in a prime position to launch a campaign in their communities to inform those seeking help and their families about the gap between what is being offered to patients and what is actually known to be effective at preventing relapse and death. Patients deserve the opportunity to make a well-informed choice about which path they take to recovery.

We should shift the focus away from discussing the superiority of one medication approach over another toward having thoughtful, tailored discussions to better understand which medication treatment option can best match an individual patient's needs. Ultimately, as more evidence-based medication treatments are provided to patients with opioid use disorders, overdose deaths and other significant morbidity can be decreased.

Disclosures:

Dr Brezing is a Fellow in Addiction Psychiatry at the New York State Psychiatric Institute and Columbia University College of Physicians and Surgeons in New York. Dr Bisaga is a Professor of Psychiatry at Columbia University College of Physicians and Surgeons and a Chair of the mentoring program "Physicians' Clinical Support Service for Medication-Assisted Treatment." (PCSS-MAT). The authors report no conflicts of interest concerning the subject matter of this article.

The PCSS-MAT is a national training and mentoring project developed in response to the prescription opioid misuse epidemic and the availability of newer pharmacotherapies to address opioid dependence. The overarching goal of PCSS-MAT is to make available the most effective evidence-based education and training resources about medication-assisted treatments to serve patients in a variety of settings, including primary care, psychiatry, and pain management. The PCSS-MAT mentors are a national network of trained providers with expertise in medication-assisted treatment and who are skilled in clinical education. The PCSS-MAT mentoring program is available at no cost to providers. Funding for this initiative was made possible by a grant from SAMHSA (Substance Abuse and Mental Health Services Administration).

FREE WORKSHOP

On

Anger Management

at Karachi Psychiatric Hospital

28-11-2015

Karachi Psychiatric Hospital held the monthly workshop.
Topic: ANGER MANAGEMENT

NIFAZ-E-URDU

16-08-2015

بابائے اُردو مولوی عبدالحق کی برسی کے موقع پر سینیٹر تاج حیدر، کمشنر کراچی شعیب احمد صدیقی، سرپرست اعلیٰ تحریک نفاذ اُردو ڈاکٹر سید مبین اختر، صدر نسیم احمد شاہ اور دیگر فاتحہ خوانی کر رہے ہیں۔