“He’s addicted to ‘Fortnite’!” is a chief complaint I have heard numerous times over the past 2 years in my treatment of children and adolescents. However, even before “Fortnite” became a household name, I was seeing young patients for whom gaming had transformed into something far more serious than a carefree pastime. It was almost becoming a recognizable pattern: child starts playing a videogame, child won’t stop playing videogame, parents remove access to videogame, child flies into a rage with sometimes terrifying consequences. Yet, while this pattern was often predictable, it was difficult to name.

Depression, anxiety, suicidality
A systematic review and meta-analysis examined the risk of adolescent cannabis use in the development of major depression, anxiety, and suicidal behavior. The analysis included longitudinal and prospective studies of cannabis use in adolescents aged younger than 18 years who were then assessed in young adulthood (aged 18-32 years). Eleven studies for a total sample of 23,317 adolescent cannabis users were included in the analysis.

The risk of depression (odds ratio \( OR = 1.4 \)), suicidal ideation (\( OR = 1.5 \)), and suicide attempt (\( OR = 3.5 \)) in young adulthood was significantly increased in adolescents who used cannabis compared to those who did not.

CONTINUED ON PAGE 5
Gaming Addiction

Continued from page cover

Gaming disorder seems to be a fitting diagnosis, but its existence as an independent mental health condition remains highly controversial, with many researchers and clinicians divided on this issue. In May 2019, the World Health Organization (WHO) finally took an official stance; gaming disorder will be classified as a medical illness in ICD-11. Gaming disorder should be of “sufficient severity to result in significant impairment in personal, family, social, educational, occupational or other important areas of functioning” and would “normally have been evident for at least 12 months.” Their decision is based on “reviews of available evidence and reflects a consensus of experts from different disciplines and geographical regions that were involved in the process of technical consultations undertaken by WHO in the process of ICD-11 development.”

Diagnostic controversy

WHO is arguably the most influential organization to weigh in on this debate thus far, and as such, their designation has already generated a significant amount of international criticism. Numerous representatives from the video gaming industry banded together to deliver a joint statement, stating “The World Health Organization knows that common sense and objective research prove video games are not addictive. . . . We strongly encourage WHO to reverse direction on its proposed action.” The gaming industry is not alone in its criticism of WHO’s decision.

Andrew Przybylski, experimental psychologist and Director of research at the Oxford Internet Institute responded to the proposed designation as early as last year, stating that “WHO’s tentative move to pathologize digital play is premature.” In 2017, Przybylski and more than 20 other researchers published an open debate paper responding to the possible ICD-11 designation; they expressed concerns that with this designation, individuals who play video games without developing pathological use will be inappropriately stigmatized. However, criticism of gaming disorder goes well beyond concerns regarding its potential impact on “healthy” gamers.

Preliminary evidence for pathological gaming

One criticism against making gaming disorder an independent disorder is that the neurobiological consequences of other addictive disorders are extensively documented, while those associated with gaming disorder are not. Imaging studies of gaming disorder are few and have significant design limitations (eg, homogenous samples, wide diversity in type of gaming).

However, despite the undeniable need for additional research, preliminary evidence does suggest possible behavioral and physiological changes from increased gaming. Individuals meeting criteria for internet-gaming disorder (IGD) appear to exhibit decreased loss sensitivity, enhanced reactivity to gaming cues, and aberrant reward-based learning, similar to changes seen with pathological gambling behavior. Neuroimaging studies, specifically fMRI, also indicate changes in brain regions associated with addiction, rewards, and emotional processing; compared with controls, individuals with IGD have increased activation in areas such as the nucleus accumbens, amygdala, anterior cingulate, dorsolateral prefrontal cortex, and insula. Moreover decreased gray matter volumes have been found in the cerebellum, orbitofrontal cortex, anterior cingulate cortex, and supplementary motor area of individuals with IGD.

These neurobiological changes may be more pronounced for certain types of video games, specifically related to how reward delivery is designed within a game. For example, many popular video games now include “loot boxes,” where gamers can pay real money to purchase a random selection of virtual rewards. The gamer hopes that in that selection will be a highly sought-after reward of great value within the video game itself. The trick is that like the slot machine, the odds of obtaining a valuable item are both unpredictable and slim, prompting the gamer, in essence, to gamble. Loot boxes are not the only method video game designers use to perpetuate gaming, but the sheer number of, and variability between, video games makes it tremendously difficult to generalize neurobiological findings to all individuals with pathological gaming issues.

Limited treatment options

Another potential barrier to recognizing “gaming disorder” is that there are limited treatment options for the disorder. There is a long-standing adage in medicine that once a physician officially recognizes and documents a problem, the onus is then on the physician to figure out how to fix it. For gaming disorder, the lack of standardized research makes treatment decisions exceedingly challenging.

What little evidence there is suggests that treatment options similar to those used in addictive disorders (eg, bupropion, cognitive behavioral therapy) may provide some benefit, and that treating comorbid conditions (eg, ADHD, depression) may be helpful. However, in order to discern effective treatment options for IGD, a standardized definition, diagnosis, and screening method are crucial; therefore, without international recognition of IGD and subsequent standardization of diagnostic criteria and screening, treatment studies will likely continue to be inadequate.

Pathological gaming as a stand-alone diagnosis

Perhaps the most significant debate over the existence of IGD relates to the question of whether pathological gaming and internet use are associated phenomena resulting from mental health disorders, rather than separate entities. IGD has been found to be comorbid with numerous psychiatric diagnoses, including depression and anxiety. A 2016 study found low intercorrelation between addictive online variables and evidence that psychiatric diagnoses contributed significantly to any noted variance between addictive internet and gambling behaviors.

Regardless of these findings, there are few diagnoses that exist in true isolation in psychiatry, and even if pathological gaming is the result of a preexisting psychiatric disorder, a teenager who begins engaging in pathological behavior and help address it, just as we would help manage binge eating or cannabis use disorders—whether maladaptive coping skills or stand-alone diagnoses.

Pathological gaming and psychiatric symptoms

Certainly, there are valid points in support of and against the creation of a gaming disorder diagnosis, but it is pathological gaming’s impact on our patient population that should prompt attention from the field of psychiatry. While the percentage of total gamers that meets proposed gaming disorder criteria appears quite small, the noted comorbidity between psychiatric diagnoses and pathologic gaming suggests that individuals who meet IGD criteria may be more likely to be our patients. As psychiatrists we must recognize this pathological behavior and help address it, just as we would help manage binge eating or cannabis use disorders—whether maladaptive coping skills or stand-alone diagnoses.

Psychiatry’s recognition of the disorder is especially important considering that pathological gaming may have a more negative impact on those with existing psychiatric illness. Among individuals seeking treatment for IGD, those with higher scores on baseline Beck Depression Inventory (BDI) rating scales required extended IGD treatment and individuals who endorse comorbid ADHD symptoms also appear to have more severe IGD.

Thus, while support of a gaming disorder diagnosis might risk stigmatizing or incorrectly assigning pathologic behavior to healthy gamers, it might also help to advance international knowledge of IGD in vulnerable populations with comorbid psychiatric illness. Moreover, WHO’s designation of gaming disorder may also be a necessary first step toward improving research on internet addiction, or problematic internet use (PIU). PIU research is similarly plagued by use of many different diagnostic criteria and screening tools although individuals with PIU alone appear to be in a different demographic than those with gaming disorder, with different comorbidities (eg, individuals with only gaming disorder are more likely to be male). PIU similarly appears to pose a unique risk to those with existing psychiatric illness. For example, psychiatrically hospitalized adolescents with PIU are more likely to exhibit both suicidality and aggression than psychiatrically hospitalized adolescents without PIU.

Conclusion

If the American Psychiatric Association decides to follow WHO’s example and officially recognize gaming disorder in DSM, they will be making an important statement of national support for funding of well-designed studies to elucidate further the effects of digital media on patients. Critics of WHO’s recognition of gaming disorder attribute the designation in part to its caving under political pressure from Asian countries, some of which have been pushing for formal recognition of gaming disorder for years. Gaming addiction has become a significant public health concern in countries like South Korea, with governments going so far as to enact public policies and laws to target the problem.

While it’s true that gaming in the US has not yet become the crisis that it has become in other countries, DSM inclusion of the disorder might similarly help to inspire interventions beyond the level of the individual here in the US, ideally including policy proposals for primary prevention. American politicians are already taking notice of gaming and internet addiction. The most notable example is the CAMRA Act, a bipartisan bill drafted by congress in 2018 that proposes the allotment of $95 million for government funding to the NIH in support of projects studying the effects of technology and media on youth.
The internet and video gaming are not going away, and game designers will continue to prioritize habitual gaming over the health of players, leaving the burden of pathological gaming on users and their families. For one couple in South Korea, the burden was the death of their infant child when they neglected the child’s care in order to play video games.13 For a mother in Ohio, it was the loss of her son played Halo, reportedly for up to 18 hours a day; when she took the game away in disapproval, her son shot and killed her.14

While these examples are rare and extreme, not every individual who drinks alcohol drinks to the point of cirrhosis, and yet we screen for alcohol use regularly, assessing for when social use has become an alcohol use disorder. For many of our patients and their frustrated parents, the risks of psychiatry’s continued avoidance of a potential gaming disorder may already be too high.

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Cannabis Use

Continued from cover

higher in adolescent cannabis users than in nonusers; a significantly increased risk was not found for the development of anxiety disorders (odds ratio = 1.2). It is important to note that the increased risk of depression and suicidal behavior in young adulthood was present even in the absence of a premorbid psychiatric condition. Based on this study, the researchers concluded that the estimated population attributable risk of depression from cannabis use is 7.2% in adolescents; approximately 413,326 cases of adolescent depression are potentially attributable to cannabis use.

Age, cannabis use frequency, and mental health problems

The effects of age on cannabis use frequency and cannabis use disorder on psychotic, depression, and anxiety symptoms in adolescents and adults were evaluated by Leadbeater and colleagues.7 A randomly recruited sample of 662 adolescents aged 12 to 18 years was assessed over a 10-year period.

More frequent cannabis use was significantly associated with more depressive symptoms from ages 16 to 19 and after age 25. Furthermore, cannabis use was significantly associated with psychotic symptoms after age 22. There was no association between frequency of cannabis use and anxiety symptoms in the study sample. With regard to cannabis use disorder, there was an association with higher depressive symptoms at ages 19 to 20 and at age 25; psychotic symptoms after age 23 were associated with adolescent cannabis use disorder. Cannabis use disorder was also associated with higher anxiety symptoms at ages 26 to 27.

Adolescent cognitive development

Morin and colleagues examined the relationship between cannabis use and cognitive development in adolescents. The study sample included 164

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14. Evren C, Evren B, Dalbudak E, et al. Relation of cannabis use with premorbid psychiatric condition. For many of our patients and their frustrated parents, the risks of psychiatry’s continued avoidance of a potential gaming disorder may already be too high.
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Cannabis Use

Continued from page 6

over the past few decades, Wilson and colleagues5 reviewed the effects of increasing cannabis potency on adolescent health.

High-potency cannabis was associated with five times higher probability of having a diagnosis of a psychotic disorder compared with cannabis nonusers. Increased risk of relapse following first episode of psychosis was associated with frequent use of high-potency cannabis. In cross-sectional studies, high-potency cannabis use was associated with depression and anxiety in adolescent cannabis users. These findings are concerning because adolescents typically have little information about the potency of cannabis that they are using.

Clinical Implications

These recent studies add significantly to the evidence that cannabis use in adolescents has adverse effects on mental health with risk for depression, psychosis, and cognitive impairment, especially inhibitory control. Adolescents and their parents need to be informed about the adverse consequences of cannabis use, whether the adolescent is or isn’t currently using substances. Many psychiatric disorders increase the risk for cannabis use and conversely frequent cannabis use, especially higher potency cannabis, increases the likelihood of psychiatric disorders. With pending legalization of marijuana and increased access for adolescents, the public needs to be informed about the deleterious mental health effects of cannabis use in adolescents.

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3826 seventh graders (mean age, 12.7 years) from 31 schools in the Montreal area. These youth were assessed annually for 4 years (grades 7-10) on cannabis use, alcohol use, and cognitive functioning, including recall memory, perceptual reasoning, inhibition, and working memory. The assessments were completed via a confidential annual web-based survey during class time to assess cognition and substance use.

Adolescent cannabis and alcohol use were associated with lower working memory, perceptual reasoning, and inhibitory control. Of particular concern, cannabis use showed neuroplastic (concurrent effect) and neurotoxic (lasting effect) of cannabis, which was not found for alcohol use. For example, when adolescent cannabis use increased in frequency in a given year, there was a reduction in delayed recall memory and perceptual reasoning in that same year.

Cannabis use in a given year was also associated with impaired inhibitory control and working memory a year later. These findings are particularly worrisome given that cannabis use in this sample was low and infrequent, yet cognitive changes were detected with small increases in cannabis use.

Decreased threat responsiveness as a function of cannabis use disorder has been reported in adolescents.8 Eighty-seven adolescents with cannabis use disorder and/or alcohol use disorder were scanned with fMRI during a looming threat task. During this task, adolescents showed images of threatening or neutral human faces or animals that appeared to be looming (increasing size over time) or receding (decreasing size over time).

Adolescents with higher severity of cannabis use disorder symptoms showed decreased response to looming stimuli within the rostral frontal and fusiform gyrus and amygdala. There were no associations with alcohol use disorder symptoms. The researchers speculate that decreased threat responsiveness may be a neurotoxic effect of cannabis abuse and related to conduct problems (less concern about negative consequences) associated with cannabis use disorder.

Mental health effects and increasing cannabis potency

The potency of cannabis with rising concentration of delta-9-tetrahydrocannabinol (THC) has been increasing...
Psychiatric Disorders and Pain

Steven A. King, MD, MS

The association between psychiatric disorders, most notably depression and anxiety, and pain is well established. However, mental health professionals, and especially psychiatrists, are still often excluded from treating patients with pain as many of our non-psychiatrist physician colleagues still often believe that there is little for them to do in the care of patients with pain unless it is clearly secondary to a psychiatric disorder. The results of two new studies highlight the importance of addressing mental health problems in patients with pain.

Total knee arthroplasty

The first study examined the effects of MDD on the outcomes for 260 patients who underwent total knee arthroplasty (TKA). Patients completed baseline measures before the surgery that included the Patient Health Questionnaire to evaluate the presence of MDD and others to evaluate pain, level of functioning, and overall quality of life. The testing was repeated at a year following the surgery.

The patients were divided into four groups:

1. Those who didn’t suffer from MDD either at baseline or follow-up
2. Those who suffered MDD at baseline but not at follow-up
3. Those who didn’t suffer MDD at baseline but did at follow-up
4. Those who suffered MDD both at baseline and follow-up

At baseline there were no significant differences between the groups with regard to knee function. However, there were significant differences between them at one-year follow-up. Patient with MDD at both baseline and follow-up were found to have significantly less net improvement than patients in the other three groups. Patients who did not have MDD at baseline but did at follow-up also had less improvement than patients who never had MDD or those with MDD that had resolved by follow-up. Patients in the latter two groups had similar levels of improvement.

Visser and colleagues conclude that patients with MDD can still benefit from TKA. They emphasize that the presence of the psychiatric disorder is not a contraindication to the surgery, but it is important to at least begin to treat symptoms before patients undergo TKA. Moreover, it is important to monitor the mental health of patients who have undergone the surgery to determine whether depression is developing and needs to be treated. Also noted was the difficulty in determining whether the psychiatric disorder caused the reduction in benefits from the surgery or if the reason for continuing or new-onset depression was the lower level of improvement following the surgery.

Chronic low back pain

The second study comprised 284 patients with chronic low back pain (CLBP) with or without radiculopathy who were evaluated on their first visit to chronic pain clinics in Portugal. The instruments used to evaluate patients included the Hospital Anxiety and Depression Scale (HADS), Brief Pain Inventory, and the Shortened Treatment Outcomes in Pain Survey. The latter two were again used at one-year follow-up to gauge the levels of pain and physical functioning.

During the year, the patients underwent what was described as “the usual multidisciplinary approach” to CLBP. Although the article does not include what was meant by this, it notes that among the services provided by the clinics were “general medical therapy, invasive approaches, physical therapy, and psychological assessment and/or cognitive behavioral therapy.”

At baseline, 51.4% of patients had depression and anxiety symptoms on the HADS while 21.5% had only depression, 6.7% only anxiety, and 20.4% neither. Study findings indicate that patients who suffered from both depression and anxiety symptoms at baseline had significantly worse outcomes with pain severity and disability at the one-year follow-up. The presence of either depression or anxiety alone at baseline also affected both of these measures but at a lesser level.

For many patients with chronic pain conditions... the assessment of mental health at the onset and throughout treatment is of vital importance.

The researchers concluded that depression and anxiety symptoms at the onset of treatment of CLBP were predictive of treatment outcomes even at the pain clinics where it was expected that psychological issues would be addressed.

Conclusion

Both studies highlight the potentially significant impact the presence of psychiatric disorders and/or their symptoms can have on response to treatments for chronic pain. In patients with chronic pain, the presence of depression or anxiety is often discounted as being secondary to the pain and therefore expected to resolve once the pain improves. Furthermore, because of this, once treatments for the pain are instituted, the psychiatric disorders may be ignored.

Patients with CLBP may be expected to be offered some psychologically based treatments at a pain clinic, but that is not always guaranteed. Moreover, it is much less likely that someone undergoing a TKA would be offered similar services. Even if that person was in treatment for MDD, it is quite possible that the issue of pain may not come up during treatment because patients and psychiatrists may think that knee pain and the response to surgery may have little connection with one’s mental state. Even if MDD is identified prior to surgery, it may be overlooked as a possible factor in the level of a patient’s benefits as a result of the TKA.

These studies demonstrate that for many patients with chronic pain conditions and even those who undergo appropriate surgical therapies such as TKAs, the assessment of mental health at the onset and throughout treatment is of vital importance. Without the active involvement of mental health professionals including psychiatrists in the care of patients with pain, the effectiveness of treatment may be markedly reduced.

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References

The Piccolo Player and His Last Tragic Tune

Sharon Packer, MD

Mat was big, blonde, and a bully. She was also a Buddhist who didn’t eat meat or drink beer. She called herself Mat, short for Matilda, using a gender-neutral name long before it became fashionable.

Mat was the proverbial “Big Nurse” who bulldozed residents, attendings, and even ward chiefs. Her concern for patients distinguished her from the diabolical Nurse Ratched—although some med students compared her to Nurse Diesel from Mel Brooks’s spoof, High Anxiety (1977).

Had Mat told me that she secretly called herself “Brunhild” rather than “Mat,” and dressed like a Valkyrie in private, and imagined herself leaving her day job and auditioning for an operatic role in the Ring Cycle, I would have believed her. But, to us, she was Mat, the head nurse. It is she who is the star of this story, more than I, and more than the unfortunate patient, the piccolo player, whose preliminary diagnosis surfaced through our combined efforts.

Nick, as I shall call him, was a youngish male who was sent “upstairs” from the emergency department (ED). The ED doc called, and said, “it’s probably just drugs. You know how they are . . . I couldn’t send him home in his condition, so I sent him upstairs to psyche. At least he’ll be safe there, till everything wears off.” Nick had started sobbing uncontrollably in an all-male dance hall near the hospital. “He should have been happy,” said the ER doc, who parroted the words of Nick’s friend, who said that Nick was thrilled by his Lincoln Center audition and would soon graduate from a conservatory upstate.

We assumed that Nick had been medically cleared in the ED. But there’s a reason why we should never assume, and there is no need to repeat that reason here. The timing was also telling. It was the early eighties, before medicine knew much about the plague brewing in the West Village and in San Francisco. All we knew was that Nick was too incoherent to relate a coherent story.

Unable to speak without sobbing, he pulled out his wallet, and showed his school ID. He was indeed about to become a professional piccolo player. He was not some one who set up shop on the subways, or street corners, waiting for tourists to drop tips into his hat. Hoping to learn more about him, I asked to speak with someone from home. He nodded “yes,” so I asked him to call his brother on the phone.

That’s when it became apparent that something much more was amiss. I slid the phone across the keypad, near Nick’s hand. It was a push button model in an era that had not yet envisioned auto-dial cell phones, much less speech-activated Siri. But this conservatory-trained piccolo player couldn’t dial the phone. His fingers stumbled around the keypad. His digits didn’t flip fast enough, even though he presumably had far better fine movement control that almost anyone around, save for some select neurosurgeons.

His gait was unimpaired, and his speech was clear, without slurring. The common signs of intoxication were absent. This strange sign prompted me to perform some impromptu “bedside” neurological tests even before asking the standard mental status questions used to assess memory and cognition.

Instead, I asked him to touch each finger with the opposing thumb, and then flip their hands right side up and upside down, as I observed for speed. Not surprisingly, Nick could not perform these simple tests any better than he could dial a phone. He had “dyssyadiachokinesia,” a neurological sign of cerebellar dysfunction. Whatever ailed him, it was not strictly psychiatric, and it probably was more than the recreational drugs that the ED resident suspected.

Dysdyadiachokinesia was a hard word to remember—and an impossible one to forget. The differential diagnosis for dysdyadiachokinesia was ominous: MS for starters in someone his age. Cerebellar tumors occur in much younger persons, as well as more obscure disorders, and some newer diagnoses also.

I was still contemplating the significance of this unexpected neurological sign, when Mat burst into the room, yelling, “stop.” She was a bully, for sure, but she was not an alarmist. In her hands were plastic gloves and a blue paper surgical gown, the kind that would pop up throughout hospitals soon enough. “Don’t draw bloods before you put short run. Over the next few months, more “Nicks” would arrive in the ED, some with neuropsychiatric symptoms and nothing but, and some who were sick enough to enter ICU immediately. Over the next few weeks, white splotches surfaced on Nick’s skin.

If only Nick’s story ended as nicely as Mozart’s The Magic Flute, where Papageno the bird catcher meets his partner. But that was not meant to be. It was painful to imagine Nick’s last act. At very best, he entered Valhalla as heroically as the deities who died in Wagner’s opera, after the skies blazed red like fire.
FROM THE EDITOR

A Drug’s Journey: From the Pill Bottle to the Toilet

John J. Miller, MD | Editor in Chief

A mythology exists that creates one of the most significant nemes for the practicing clinician in psychiatry: drug formularies that impose drug dosage and dispensing limitations that quite often result in an unnecessary and burdensome obstacle to our goal of effectively treating patients. Many of us older psychiatric clinicians reminisce back to a time absent of drug formularies when we could dose a medication unencumbered to maximize the benefit to our patient. Sadly, we have surrendered our power to the insurance magnates who pretend to be more knowledgeable than we are about the medication choices and doses that will provide the best treatment—and hence outcome—for our patients.

A medication’s dosage used in phase 3 clinical trials is chosen to create the highest likelihood of clinically significant separation from placebo, while minimizing adverse effects. Additionally, as required by the FDA to create as clean a treatment population as is possible, participants in clinical trials are not illustrative of the patients we treat on a day-to-day basis in our clinical practices. For most phase 3 clinical trials, subjects can have no psychiatric comorbidity, no significant medical problems, no recent or active substance use disorder, and no serious acute symptoms. They cannot be pregnant, must be of a specific age range, and must be competent to understand and consent to the treatment protocol—and this is just the short list.

The enrollment requirements would exclude more than 90% of the patients that I have treated at Seacoast Mental Health Center, where I have practiced for the past 12 years.

It is only after a medication is FDA approved, and we prescribe it to hundreds of thousands of patients—all with unique factors that will determine a serum drug level for each individual patient—that we learn the true clinical range of a new drug. Two common examples of this are risperidone, which we initially dosed too high (based on the FDA approved initial product insert), and ziprasidone, which we initially dosed too low (based on the FDA approved initial product insert). In a time when cost savings is the driving force behind insurance company policies, it would seem wise and prudent to allow treating clinicians to choose the medication they deem most appropriate for a specific patient, and dose it as aggressively as is clinically indicated to improve the patient’s symptoms and functioning and minimize toxicity to the brain.

Let us look at the many variables, unique to each patient, that influence a medication’s serum level. In clinical reality, it is the serum level of the drug, and not the dose of the drug, that determines clinical response. So, let us follow the journey of a drug from the pill bottle to the toilet.

**Getting the medication into the body**

The first step in the process of getting a clinically effective drug level is getting it into the body. The best route of administration is determined by the many pharmacokinetic and pharmacodynamic properties of the drug. The most common delivery system is that of oral administration, where the medication is simply swallowed. Even with this route of administration significant rules may apply to obtain consistent and adequate serum levels. One common example is that of levethroxamine, which needs to be taken on an empty stomach. Other drugs may require the presence of a specific number of calories to maximize absorption, or a specific pH of the stomach.

Other drugs are best administered sublingually. This route of administration in some cases is required. The classic case in psychiatry is asenapine, which is primarily metabolized by a phase 2 enzyme that is highly prevalent in the gut. If asenapine is swallowed, up to 99% of it is transformed into an inactive metabolite by UGT (uridine 5-diphosphate glucuronosyltransferase 1A4 (family = 1, subfamily = A, gene = 4)). To maximize sublingual absorption, the tablet is kept under the tongue for 10 minutes, and ideally no swallowing occurs during this time.

In most cases, the fastest way to get a drug into the body is through intravenous injection, which usually results in the highest bioavailability of the dose. A close second is administration through intramuscular injection and subcutaneous injection. These two routes of administration are often used to inject drugs available in a long-acting delivery system that can allow for weekly, monthly, bi-monthly, and even tri-monthly administration.

Another route of absorption shown to have advantages for various clinical and pharmacological reasons is transdermal administration, whereby a transdermal matrix/patch is adhered to the skin that releases the drug. Examples include selegiline, nicotine, rivastigmine, buprenorphine, and methylphenidate. Additional delivery systems include intranasal spray and nebulizer inhaler.

**Absorption from the gastrointestinal tract**

Early in drug development, it is determined what the best route of administration is for a specific drug. Some drugs have multiple routes of administration, which provides a broader range of options to better suit clinical variables. Currently, oral drug administration remains the most common route, and creates a wide range of absorption variables that can significantly affect how much or how little drug actually makes it into the body’s circulation.

The first challenge is keeping the drug intact as it moves through the stomach. Variables include the pH of the stomach, the rate of gastric emptying, and in some cases, drug absorption by the stomach. If a patient has had gastric surgery, including gastric bypass/stapling/lap band placement, the result can be a “dumping” syndrome where the drug’s visit in the stomach is all too brief. When I have a patient scheduled for gastric bypass surgery, I check a 12-hour post-dose serum level of all of the drugs that I prescribe to get a baseline serum level before the mechanics of the stomach are forever altered. One month post-gastric bypass I repeat these drug levels, which allows me to adjust the dose to recreate the serum level the patient had been previously stable on.

Once passage through the stomach is complete, next is the long and winding road through the small and large intestines. Many of the body’s drug metabolizing systems exist in the intestines, as well as the liver and other organ systems. Three primary drug metabolic processes are already at work at the lining of the gut: P-glycoprotein activity, phase 1 cytochrome P-450 metabolism, and phase 2 conjugation. This makes sense, as the site of absorption by the gastrointestinal (GI) tract is the perfect location for a first-line defense against potentially toxic molecules. P-glycoproteins serve to pump back out into the gut lumen potentially dangerous molecules, and phase 1 and phase 2 metabolism serve to inactivate through enzymatic drug modification any potentially toxic molecules ingested by the local food sources.

Transit time through the intestine can dramatically alter drug absorption. A patient with irritable bowel syndrome with rapid transit time may see an intact medication tablet or capsule mixed in with his or her stool. This can be more common with an extended-release delivery system. Certain food products, or other medications may bind to a drug and carry it further down the GI tract where absorption is poorer.

**Drug metabolism**

As many will remember from anatomy class, the superior and inferior mesenteric veins, which carry all substance absorbed by the intestines, merge with the splenic vein to form the portal vein, which then filters its content through that great metabolic factory—the liver. This first-pass metabolism process provides the metabolic pathways to modify drug structures to be more water soluble, so they can eventually leave the body through renal excretion, or in other cases adds various structures to enhance passage out with the bile. There are two primary types of metabolic pathways:

(CONTINUED ON PAGE 18)
Mixed Features, Suicide, and Adolescents at Risk

**SIGNIFICANCE FOR PRACTICING PSYCHIATRISTS**

- To diagnose a pure unipolar major depression in an adolescent (or adult), first rule out mixed features and prior hypomanic/manic episodes.
- Obtain a detailed family history.
- Obtain the developmental course of symptoms.
- Remember that treatment is only as good as your diagnosis.

**TABLE 1. DSM-5 non-overlapping mixed feature criteria**

- If an individual is predominantly manic or hypomanic but also presents with depressive symptoms, the mixed features specifier may be considered. Depressive symptoms may include depressed mood, diminished interest or pleasure, slowed physical and emotional reaction, fatigue or loss of energy, and recurrent thoughts of death. At least three of these symptoms must be present nearly every day during the most recent week of a manic episode or during the most recent four days of a hypomanic episode.
- Conversely, if an individual is predominantly depressed with some manic or hypomanic symptoms, the mixed features specifier may also be considered. These manic or hypomanic symptoms may include elevated mood, inflated self-esteem, decreased need for sleep, and an increase in energy or goal-directed activity. At least three of these symptoms must be present nearly every day during the most recent 2 weeks of the major depressive episode.

**Adolescents at Risk**

> Hunter Yost, MD

A ssessment of suicidal risk in adolescents is a solemn professional obligation that involves obtaining as much information as possible from family members or caregivers. Evaluation of mood disorders is an essential part of the assessment.

When DSM-V took a significant step beyond previous editions to include the mixed features specifier for unipolar major depression, the already contentious area of child and adolescent mood disorders became even more challenging. It is also an opportunity, however, to expand our understanding of mood disorders and to provide safer treatment for affected youths.

**What’s past is prologue**

Numerous authors have reviewed Kraepelin’s original conceptualization of mixed features. In recent decades, research on mixed features has re-established Kraepelin’s thinking and has provided insights that challenge established dogma about depression and mania and show how overlooking mixed symptoms can increase suicide attempts and completed suicides in adolescents and adults.

Another major contributor to our understanding of mixed features in depressive states is Athanasios Koukopoulos. Verdolini and colleagues placed one of Koukopoulos’s core criteria, mood lability (or affective lability), which they define as “the predisposition to rapidly reversible and marked shifts in affective states that are extremely sensitive to environmental events with intense behavioral responses” as distinguished from DSM-defined “mood reactivity” in response to positive stimuli, near the center region of their Revised Affective Spectrum that bridges the continuum from pure depression to pure mania. These researchers explain that affective lability was excluded from the DSM-5 “with mixed features” specifier, possibly leaving many cases of mixed depression undiagnosed and subsequently inadequately treated.

**Studies clearly indicate that mixed presentations are the rule rather than the exception in adolescents:**

- “This study showed that bipolar spectrum disorders in youth are episodic disorders most often characterized by subsyndromal episodes and, less frequently, by syndromal episodes, with mainly depressive and mixed symptoms and rapid mood changes.”
- “The mixed state was the most common presentation for bipolar adolescents who were in the midst of an MDE at the time of presentation to a mental health clinic.”
- “Mixed hypomania was a common phenomenon in pediatric bipolar II patients.”

**Mixed features: non-overlapping vs overlapping**

What counts as a mixed feature? DSM-5 has expanded the concept substantially over DSM-IV, allowing the specifier to be used for both depressive and manic episodes yet restricting it to three symptoms each of the opposite pole of 4 days’ duration or 2 weeks’ duration, respectively (Table 1). The non-overlapping mixed feature criteria have limited support in the literature.

In contrast, the so-called overlapping criteria listed in Table 2 are supported in the literature. Given that the majority of adolescents present as depressed with mixed features rather than with pure depressive or manic episodes, our assessment of youth at risk may need to extend beyond currently defined DSM mixed criteria.

Baláz and colleagues concluded: “Irritability and psychomotor agitation were the strongest predictors of suicide attempt. From a public health standpoint, our data highlight the necessity of detecting and treating mixed (bipolar) depression in the prevention of suicidal behavior.”

**Other studies also underscore the link between mixed features and suicide:**

- “More prevalent in suicidal versus non-suicidal subjects by multivariate analysis were: depressive symptoms, hyper-emotionality, younger-at-first-affective-episode, family suicide history, childhood mood-swings, and adolescence low self-esteem.”
- “Those with MDD and mixed features were 5 times more likely to experience suicidal ideation and 3 times more likely to engage in suicidal behavior, both of which were statistically significant increases.”
- “Suicidality might be conferred by a combination of both the excited (mixed) depressive and agitated
(melancholic) clusters,” and, “Our analyses delineate a mixed depressive substrate at risk for suicidality.”

All too frequently in the medical record there is a lack of consideration of the course or trajectory of prodromal symptoms. Faedda and colleagues10 write: “Precursors of bipolar disorder include mood lability, subsyndromal and major depression, subsyndromal hypomanic symptoms with or without major depression, cyclothymia and bipolar not otherwise specified, major depression with psychotic features, and other psychotic disorders. Bipolar disorder was also predicted by juvenile onset of major depression as well as frequency and loading of hypomanic or depressive symptoms.” This suggests that mixed features may precede and predict a bipolar disorder. Ghaemi6 considers the course of prodromal symptoms to be the most important diagnostic validator in conjunction with family history.

Screening tools
While there are screening tools to elicit bipolar symptoms—such as the MDQ for Parents of Adolescents, Young Mania Rating Scale, University of Pittsburg Risk Calculator for Kids, Parent General Behavior Inventory (GBI), and Parent-Child Mania Rating Scale—until recently there have been no screening tools for mixed features. Tavormina11 writes: “The knowledge of the clinical features of the mixed states and of the symptoms of the ‘mixity’ of mood disorders is crucial: to mis-diagnose or mis-treat patients with these symptoms may increase the suicide risk and worsen the evolution of mood disorders. The rating scale ‘G.T. MSRS’ has been designed to improve the clinical effectiveness of both psychiatrists and GPs by enabling them to make an early ‘general’ diagnosis of mixed states.” This scale awaits further validation but is noteworthy for an increased recognition of mixed features.

Sani and colleagues12 have provided validation for the Koukopoulos Mixed Depression Rating Scale (KMDRS): “KMDRS was a reliable and valid instrument to assess MxD (mixed depression) symptoms.”

Treatment
In the past, the standard of practice was to treat any symptoms of depression with an antidepressant. Often this would occur without an adequate differentiation between unipolar and bipolar depression. The new paradigm elaborated by Stahl and colleagues13 is to treat any subsyndromal manic symptoms and/or dysphoric agitation with an antipsychotic and/or mood stabilizer rather than an antidepressant. While there are no FDA-approved medications for mixed features, treatment guidelines for bipolar depression are probably most applicable to depression with mixed features.

There is general consensus that antidepressants are contraindicated as monotherapy when clear manic symptoms are present; however, consensus is less clear as to the role of antidepressants in the presence of mixed features or even the existence of mixed features in a given adolescent. Koirala and associates14 conclude: “Findings of the study indicate that a substantial proportion of young MDD subjects share BPD illness characteristics. These high risk subjects, if treated with antidepressants, need to be monitored for development of BPD.” In addition, Akiskal and colleagues15 note that “reports of increased risk of suicidal ideation and/or behavior in some depressed patients treated by antidepressant monotherapy or combinations thereof might be attributed to baseline psychomotor activation/agitation as part of an unrecognized bipolar mixed state.”

Because of the significantly elevated risk of suicide in adolescents with mixed features, it would behoove psychiatrists to err on the side of overdiagnosing mixed features and considering mood stabilizers and/or second-generation antipsychotics as first-line therapies.

(Continued on page 18)
Mergers and More Rock the Pharmaceutical Industry

Heidi Anne Duerr, MPH

From drug company mergers to government watchdogs, important trends as the pharmaceutical industry balances the need for innovation with the need for financial support for that innovation are emerging this summer.

AbbVie announced the $63 billion acquisition of Allergan, which would make the new company a $48 billion enterprise.1 While AbbVie’s current top-selling drug is Humira (adalimumab), it has recently invested in neuroscience, investigating potential drugs for Parkinson disease, multiple sclerosis, and Alzheimer disease. Meanwhile, Allergan has concentrated on oncology, virology, and neuroscience products. Allergan’s current neuroscience lineup includes Vraylar (cariprazine), Viibryd (vilazodone), Saphris (asenapine), Fetzima (levomilnacipran), Namenda (memantine), and Namzaric (memantine and donepezil).

The merger could have a positive impact on the psychiatric drug pipeline, which has been largely ignored in the recent past. In a note to investors, Canaccord Genuity analyst Sumant Kulkarni shared, “We are encouraged by the focus that ABBV [AbbVie] is placing on AGN [Allergan]’s neurology/psychiatry assets.” He added that the neuroscience market drugs could get more competitive because of this merger, since the combined companies are expected to invest in migraine and schizophrenia/bipolar depression candidates.

“We believe this deal brings some attention back to the scarcity value of later-stage/filed neuro-related assets,” Kulkarni wrote. “While several major pharmas have deemphasized neuroscience, ABBV is one that has a presence in neuroscience, which will get even larger if the AGN acquisition closes.”1

Other recent mergers include Bristol-Myers Squibb and Celgene, Pfizer and Array BioPharma, Eli Lilly and Loxo Oncology, and Roche and Spark Therapeutics.2

Accusations against UK antidepressant suppliers

In the United Kingdom, four antidepressant suppliers found themselves in hot water with the Competition and Markets Authority (CMA) regarding anti-competitive conduct. The CMA accused King Pharmaceuticals and Auden Mckenzie of “sharing out” the antidepressant nortriptyline, with Auden Mckenzie only supplying 10-mg nortriptyline tablets while King only supplied the 25-mg tablets. The agency also accused King, Alissa, and Lexon of “exchanging commercially sensitive information, including information about prices, volumes and entry plans, to keep Nortriptyline prices high.”3

Evergreening bill introduced

On this side of the pond, legislators took aim at the pharmaceutical industry tactic known as “evergreening,” in which companies make minor changes to a popular drug and file for patents to extend their exclusivity and higher prices. Introduced by Representatives Hakeem Jeffries (D) from New York and Doug Collins from Georgia (R), the bipartisan Terminating the Extension of Rights Misappropriated (TERM) Act of 2019 places the burden of proof on the pharmaceutical companies to demonstrate “distinct inventions” to qualify for a new patent. “The bipartisan TERM Act will curb patent abuses in order to expedite the entrance of lower cost generic drugs to market,” explained Jeffries.4

Pharmaceutical companies are great innovators that create life-saving cures and treatments for families everywhere,” added Collins. “Unfortunately, some manufacturers simply file additional patents to delay generic drugs from coming to market. I co-sponsored the TERM Act to make it easier and fairer for generic pharmaceutical companies to challenge trivial patents, which ultimately means that patients get access to more drug options faster.”

Judge blocks direct-to-consumer rule

All this comes about as President Trump’s attempt to control drug prices in the US met failure. Through his health care initiatives, the Department of Health & Human Services (HHS) issued a rule in May that direct-to-consumer (DTC) advertisements must note the prices of drugs exceeding $35 per month if those drugs are covered by Medicare and Medicaid.5 The goals were to inform patients of costs and to put pressure on pharmaceutical companies to keep prices in check.

In presenting the rule in May, HHS Secretary Alex Azar (and former president of the Eli Lilly US division) said, “Patients have a right to know [the prices of medications], and if you’re ashamed of your drug...
prices, change your drug prices. It’s that simple.”

Not surprisingly, the industry did not take the rule lightly. Eli Lilly, Merck, Amgen, and the Association of National Advertisers (ANA) filed a joint lawsuit alleging that the HHS rule was unconstitutional and infringed on their First Amendment rights to free speech. They also argued that the cost may change from patient to patient, as the out-of-pocket costs vary depending on insurance coverage and other programs; this, in turn, could mislead consumers. ANA and the companies argued that it was not in the purview of HHS to make the ruling. Ultimately, US District Judge Amit P. Mehta agreed with ANA and the pharmaceutical companies.

To be clear, the court does not question HHS’s motives in adopting the … disclosure rule,” explained Mehta in blocking the HHS rule. “Nor does it take any view on the wisdom of requiring drug companies to disclose prices. That policy very well could be an effective tool in halting the rising cost of prescription drugs. But no matter how vexing the problem of spiraling drug costs may be, HHS cannot do more than what Congress has authorized. The responsibility rests with Congress to act in the first instance.”

For their part, the pharmaceutical industry seemed pleased with the outcome. “We believe strongly in providing patients and their caregivers the meaningful information they need to make informed health care decisions. That is why we initiated this action,” a Merck spokesman said in a statement following the ruling. A Lilly spokesperson added, “We are committed to working with stakeholders across the health care system to find better solutions for the larger issue, namely, lowering out-of-pocket costs for Americans who still struggle to pay for their medicines.”

Credit should be given to the Pharmaceutical Research and Manufacturers of America (PhRMA) for being proactive on DTC advertising and pricing. In October 2018, they enhanced their 2006 voluntary DTC principles, Guiding Principles on Direct-to-Consumer Advertisements About Prescription Medicines. The principle states:

All DTC television advertising that identifies a medicine by name should include direction as to where patients can find information about the cost of the medicine, such as a company-developed website, including the list price and average, estimated, or typical patient out-of-pocket costs, or other context about the potential cost of the medicine.

It is interesting to note that Eli Lilly was the first company to add pricing information. They currently list cost information for six of their branded pharmaceuticals.

What’s next?

What’s next is anyone’s guess. Caitlin Oakley, HHS spokesperson, noted that the administration “will be working with the Department of Justice on next steps related to the litigation.” Meanwhile, Senate Finance Committee Chairman Chuck Grassley (R-Iowa) and Senator Dick Durbin (D-IL) have introduced a bipartisan transparency bill that would require pharmaceutical companies to list prices of their prescription drugs in DTC advertisements. And the ANA’s Group Executive Vice President for Government Relations added, “ANA will continue to vigorously uphold the vital First Amendment rights of the advertising community.”

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Neuroprotective Effects of Antidepressants in First-episode Schizophrenia

Brian Miller, MD, PhD, MPH

Negative symptoms, subthreshold depressive symptoms, and functional impairment often persist in patients with first-episode schizophrenia (FES). Although there is evidence that antidepressants may reduce negative symptoms in patients with chronic schizophrenia, they are not recommended for maintenance treatment for patients with FES who are not depressed.1,2 No previous studies have investigated the efficacy of antidepressants for psychopathology in patients with FES.

Goff and colleagues3 hypothesized that citalopram would be neuroprotective over the first 12 months of illness and associated with improvements in negative and depressive symptoms in FES. They undertook a 52-week, randomized placebo-controlled trial of citalopram, in adjunct to clinician-determined atypical antipsychotics in patients with FES who did not meet criteria for MDD. The primary outcomes were improvement in depression as measured by the Calgary Depression Scale for Schizophrenia and negative symptoms as measured by the Scale for the Assessment of Negative Symptoms. Duration of untreated psychosis (DUP) was also considered as a predictor of response.

Participants were enrolled at one of four sites between 2010 and 2014. Inclusion criteria were a DSM IV-TR diagnosis of first-episode schizophrenia or schizoaffective disorder; aged 15 to 40 years with onset of psychosis before age 35; cumulative antipsychotic treatment for 4 to 24 weeks; no antidepressant treatment within 4 weeks; a score less than 7 on CDSS, and a score of less than 3 on the Clinical Global Impression of Negative Symptoms. Duration of untreated psychosis (DUP) was also considered as a predictor of response.

Participants who continued to meet these criteria after 4 weeks or those who scored 4 or higher on the CGI-SS or 10 or higher on the CDSS were removed from double-blind treatment and could have an unblinded prescription for an antidepressant. Data were analyzed using an intent-to-treat linear mixed model of CDSS and SANS with Area Under the Curve (AUC) as the primary outcome measures.

A total of 129 participants were screened and 95 were randomized (49 to citalopram and 46 to placebo); 73 completed 6-month assessments and 52 completed 12-month assessments, with no difference in completion rates between the groups. The mean daily dosage of citalopram was 36 mg daily and adherence rates were approximately 90% in both groups. Mean antipsychotic dose in chlorpromazine units was 374 mg daily. There were no differences in baseline demographic and clinical variables between the groups, although completers had lower psychopathology and higher cognition scores compared with non-completers.

There was a significant reduction in depression scores in the placebo group compared with the citalopram group. By contrast, there was a significant reduction in negative symptom scores in the citalopram group compared with the placebo group, particularly for the avolition subscale. A shorter DUP predicted greater placebo response for improvement in negative symptoms. Rates of new-onset depression did not differ between the groups. Sexual adverse effects were more common with citalopram, but there was no difference in overall treatment-emergent adverse effects.

The bottom line

The researchers concluded that adjunctive citalopram may reduce negative symptoms, particularly in patients with a longer DUP but was not beneficial for subthreshold depressive symptoms in patients with FES. This pattern of findings suggests a primary effect for the benefit of citalopram on negative symptoms, rather than a secondary effect of antidepressant response.

Dr. Miller is Associate Professor, Department of Psychiatry and Health Behavior, Medical College of Georgia at Augusta University, Augusta, GA. He reports that he has received research support from the NIMH, the Brain and Behavior Research Foundation, and the Stanley Medical Research Institute.

References

The Magistrates

Richard M. Berlin, MD

My musician patient in a fetal curl,
Tchaikovsky’s “Meditation” plays
an endless loop against this climate controlled
conspiracy of monitors and machines,
scattered clouds in the picture window
behind him arranged like crash cart cotton,
the volunteers’ rose garden a hemorrhage
of reds punctuated by river birch
more radiant than my white coat,
two crows perched motionless on a branch,
dusky beaks and brown eyes trained
on our window, wild magistrates
judging the way I broke bad news—
how I pressed his hand, absorbed tears,
held our silence inside Tchaikovsky’s
embrace, sky suddenly cinematic,
thunderhead crescendo, curtains of rain,
trees bowed in musical submission,
courtyard cleared, only the crows
clawed down to deliver a verdict,
room blacked out, machines mute,
midnight wings spread to cloak
a partner lit by lightning.

Dr Berlin is Instructor in Psychiatry, University of Massachusetts Medical School, Worcester, MA.
Fasten Your Seatbelts

David N. Osser, MD.
SERIES COORDINATOR

In the past several years at the VA National Tele-Bipolar Disorder Expert Consultation Program, my colleagues, Drs Eric Smith, Laszlo Gyulai, and I have been writing monthly educational newsletters for clinicians (nationwide) who have been requesting telemedicine consultation on diagnostic and treatment problems of patients with bipolar disorder or possible bipolar disorder. Over 2500 consultation requests have been received over more than 8 years and 2100 consultation notes have been delivered, so our group has developed considerable experience with this challenging disorder and the wide variety and complexity of the clinical scenarios and comorbidities that are encountered.

The newsletters are designed for easy and quick reading: all are one typed page in length, with one to three reference citations. The Editor and Board of Psychiatric Times learned of these newsletters and requested to have them published (after review) and made available to their readership. The first one follows on the right. The content of these newsletters does not reflect the position of the Department of Veterans Affairs and is solely the product of the authors.

As the coordinator of these publications, I should introduce myself. I have an appointment as Associate Professor of Psychiatry at Harvard Medical School at the VA Boston Healthcare System, Brockton Division. My area of clinical and academic expertise is in the development of evidence-derived algorithms for the psychopharmacology of psychiatric disorders, an endeavor I have been dedicated to since 1985. These algorithms have been published and republished in updated versions and (since 1995) converted to web-based applications that enable rapid and international access to the recommendations through the (free) website of the Psychopharmacology Algorithm Project at the Harvard South Shore Residency Training Program (psychopharm.mobi).

Dr Robert Patterson, a psychiatrist affiliated with McLean Hospital, created the Harvard South Shore Residency Training Program (psychopharm.mobi).

David N. Osser, MD. Consulting Psychiatrist, US Department of Veterans Affairs, National Telemental Health Center, Bipolar Disorders Telehealth Program, Brockton, MA.

About 25 collaborators on the different algorithms. It was a great privilege in 2011 to be offered the opportunity to do these consultations and see these complex patients and refine my thinking about their needs and the optimal application of the evidence-base to their care.

To introduce the columns, I begin with a few brief comments about the challenges of diagnosing bipolar disorder. On this, the evidence is clear: the condition is frequently both underdiagnosed and overdiagnosed. Patients having manic episodes may be functioning fairly well (or, as they see it, very well indeed) when manic and may not recognize or want to acknowledge the abnormal mood state, and may not seek care. Erroneous diagnoses and incorrect treatment can continue for many years.

The rate of suicide in bipolar disorder is quite high. Hence, the most important initial advice we can give readers of this column is to please pull out your DSM-5 and review the criteria for mania and hypomania. Take the time to carefully assess the patient using these criteria, looking particularly for a history of discreet episodes lasting at least 3 to 4 days. It can help to have a significant other who knows the patient well give input as to whether these discreet episodes have been occurring. Avoid making a positive diagnosis of mania or hypomania after hearing about or observing just a couple of symptoms (e.g., racing thoughts, rapid speech, tangential speech). Quick diagnosis on a hunch is a very error-prone process with bipolar disorder. Patients with rapid or overly productive speech and thoughts could have ADHD, PTSD, substance use disorders, or other problems—or all of them at once. If so, each needs to be treated separately—prioritized in order of importance.

Fasten your seatbelts. Psychiatric Times readers. There will be some surprises coming in future issues!

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References

Hyperthymic Temperament

David N. Osser, MD.

Current estimates are that 4% to 5% of the population is at risk for a disorder on the bipolar spectrum. Among the patients in the so-called soft portion of that spectrum are those with a disturbance of temperament in the direction of hypomania.

The concept of temperament is a product of German nosological research from a century ago starting with Kraepelin. In the US, the concept has been championed by Hagop Akiskal, MD and his colleagues. Akiskal is now the editor emeritus of the Journal of Affective Disorders. The notion of depressive temperament has been incorporated into DSM-5 nosology in the form of “persistent depressive disorder” (previously called dysthymia). The other pole was called hyperthymia by the Germans. DSM committee members have considered adding hyperthymia but have not done so. The research base on it is still, to many, unconvincing. However, it seems that in clinical practice one encounters individuals who have chronic low-grade hypomanic symptoms—high energy, need for less sleep than others, chronic optimism, chronic risk taking. These individuals can be prone to major depressions and can become severely suicidal.

Akiskal and colleagues have been describing these patients for almost 40 years. Their research criteria for hyperthymic temperament include onset before age 21, habitual sleep of less than 6 hours even on weekends, excessive use of denial, and traits (described originally by Schneider et al) that include being overoptimistic, self-assured, grandiose, overtalkative, warm and people-seeking, uninhibited, promiscuous, and meddlesome. Neurobiological studies have suggested the individuals have dopaminergic dysregulation.

Treatment issues have focused on what medications to use when hyperthymic individuals become depressed. The studies have all been uncontrolled. However, it seems that antidepressants are ineffective for these depressions and often trigger a mixed state or frank mania at times. Mood stabilizers and medications effective for bipolar depression may be more appropriate for the depressions in hyperthymic temperament patients.

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Mood stabilizers and medications effective for bipolar depression may be more appropriate for the depressions in hyperthymic temperament patients.

References
Adolescents at Risk

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Dr Yost provides telemedicine psychiatric services in several states for both adults and adolescents in hospitals and clinics. He reports no conflicts of interest concerning the subject matter of this article.

References
We remember the goal: making psychiatric care more available, accessible, and affordable while maintaining the highest standards. We remember the challenge: accomplishing this with limited resources. What we forget is the role played by our bad habits back then, our unverified claims of effective treatment, our poor record keeping and interminable therapeutic process had the unintended consequence of souring intra-institutional collaboration. Our new language of smoke and mirrors had the effect of souring intra-institutional collaboration.

Our new language of smoke and mirrors

We psychiatrists, for whom the clarity of words and their meaning traditionally held center stage, were now finding ourselves helpless to challenge an emerging vocabulary that peddled misinformation and bias and that compelled us to become unwitting carriers of misleading euphemisms and bogus concepts.

1. **The patient as consumer.**

With medical practice now a business and with profit the dominant ethic, truth-in-advertising was monitored, and placebo fell out of use. Patients were now consumers, presumably to spare them the indignity of the label, patient, and doctors became service providers, to help dispel their elitist image. However, this new product labeling process had the unintended consequence of what was jokingly called the medicalization-of-life, where half the population would one day be in therapy with the other half. Activities, from art to exercise to assistance finding work to assistance in obtaining affordable housing, began appearing, not as part of a service plan but as part of a treatment plan, while teachers of language, art, and exercise were beginning to self-identify as language therapists, art therapists, and exercise therapists.

Behavioral health replaced mental health, signaling that it was how a person behaved—not how he or she thought or felt—that became the core issue requiring attention (see #4 Chemical restraint).

2. **Blurred boundaries.**

Social workers began suggesting medications and dose changes as did case managers in lieu of reporting observations—their particular asset—with the hurried prescribing doctor dutifully if mindlessly making the recommended medication adjustments. Case managers and coordinators identified adverse medication reactions as allergic reactions, which then became part of medical records and, not surprisingly, tilted subsequent emergency department (ED) interventions accordingly. Also, they not uncommonly copied doctors’ orders incorrectly with patients receiving incorrect doses, even incorrect medications. Quality control was nowhere; empowerment overreach—everywhere.

3. **The fiction of confidentiality.**

When prescriptions were phoned in, one had to provide evidence of medical necessity to ensure payment, and for that the insurer had to know the medication’s purpose. But, because the word purpose was unwisely considered interchangeable with diagnosis by our non-medical handlers, the hospital and clinic staffs, including doctors and clerical staff, were routinely and inappropriately directed to phone in diagnoses, a personal detail neither required nor requested and in clear violation of patient confidentiality. The irony was seeing hospital and clinic walls and elevators replete with signs: “Patient Confidentiality Is Our Priority.”

4. **Chemical restraint.**

A lawyer’s metaphor applied in his courtroom argument against forced antipsychotic medication for his client (a case he won), along with his glib description of psychotic talk as creative speech, became enshrined in case law in Massachusetts. As a result, the concept of chemical restraint took on a mantle of literal reality, even among psychiatrists. Most psychiatrists, of course, understood that antipsychotic medications don’t act as physical restraints, they restore one’s thinking and the person does the restraining him or herself. But we nevertheless abetted the spread and legitimization of this false belief by applying the term, chemical restraint, in our practice and on official medical forms.

How could such endorsement of a blatantly bogus concept, along with its misleading language, not promote the perception that a psychiatric hospital’s principal objective was managing risky behaviors and, as such, was an instrument of social control? And how could such a perception that we psychiatrists were essentially managers of behavior for social control not suggest a political agenda on our part? More than a few former patients had already begun viewing psychiatry as dangerous, psychiatrists as their enemy, and themselves as survivors.

5. **Contracts for safety.**

This important and useful contract, a promise not to hurt oneself, signed by a patient feeling suicidal, along with his or her trusted therapist, was a sensible and effective intervention to help that desperate person keep going, hang in there until the next appointment. How was expecting such a distressed person to sign such a contract with a total stranger in an ED anything more than a gesture to protect emergency staff and the hospital from liability?

6. **Informed consent.**

And then this orphan member of our psychiatrist family to-do list. This term, with origins in a patient’s permission for a surgical operation, meaning for an invasive procedure, translates delicately to psychiatric practice, which features no invasive procedures let alone hands-on contact, just questions, insights, suggestions, and prescriptions. The relevant part of that particular doctor-patient interaction and relationship centered on our taking into account our patient’s ability to retain and process information, especially details about the medication and its effects.

That’s why consent in psychiatry, especially psychopharmacology, is essentially a process, an ongoing patient learning experience. But it rarely is. There’s no time. Instead it’s a confusing form that, some insist, the doctor signs and the patient keeps, while others insist it’s a form the patient signs and the doctor keeps. Either way it’s a one-shot affair and suspiciously like an exercise in covering one’s back (the doctor’s) and endorsing empowerment (the patient’s). What it is not is a trust-building collaborative relationship.

7. **Signing off.**

A requirement that certain medications prescribed by Massachusetts doctors had to be independently approved as appropriate led to doctors writing down their orders and then, further down the page, checking a box indicating that he or she approved of the action just taken, an action as humiliating as it is ridiculous.

Doctors were expected to sign off this way on another doctor’s meds in the absence of an identified target symptom or a form filled out by a case manager without verification for accuracy. We were expected to sign off on involuntary hospitalization forms that had information that failed to meet the legal standard for involuntary hospitalization. We were expected to sign off on medical affidavits despite disagreeing with additional content a lawyer added, and all “under pain and penalty of perjury.” We were expected...
The Changing Face of Psychiatry

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to sign off on approving things we knew nothing about (eg, ability to drive safely), sign off on meetings we never attended, and cases we never reviewed, and we were expected to make judgment calls on matters we had no way of judging (eg, capacity to sit on a jury, handle funds, use public transportation, write a will, or learn civics). It’s what team players did.

We ad-libbed (eg, in admitting a patient under commitment and being directed, as admitting officers, to check one of two boxes on the admission form to verify that the patient had either willingly signed in or had refused to sign in following an explanation of his or her rights). What do you check when the patient arrives unconscious? We asked. “It doesn’t really matter,” we were told. “No one ever reads this,” or “It’s only a signature.” Right.

We sensed that if we didn’t sign the forms as directed the job would be transferred to some non-questioning non-psychiatrist who’d be a compliant team-player. Integrity should always trump convenience, but livelihood has a way of trumping integrity.

9 Contaminating legalities. At that time, there emerged with greater intensity the operational fiction that if something is not written down it officially never happened. Conversely, if something is written down it did happen; encouraging, of course, bogus notes in records while promoting defensive practice and a culture of indifference.

10 Gaming the system. No surprise that some people suffering mental illness whose behavior fell short of behavioral criteria for hospital care (ie, danger to oneself or others or inability to care for oneself) learned to threaten danger as their key to entering a hospital for safety, relief, and healing. No surprise that that behavior was labelled, gaming the system, a notion that, ironically, both empowers and diminishes that erstwhile patient while sadly missing the point.

An unexpected and ironic dividend
Over the years we psychiatrists have discovered and demonstrated an aptitude for psychopharmacology and for contributing to its reach and effectiveness. About the placebo, it remains a transference presence. Its effect is noted and respected, but we no longer prescribe the placebo. We are the placebo.

Dr Climo is the author of Psychiatrist on the Road: Encounters in Healing and Healthcare, an account of his Locum Tenens experience.

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BookReview

Forensic Psychiatrists Explore True Crime and Family Murder

Reviewed by Karen B. Rosenbaum, MD

True crime has become increasingly popular, as evidenced by the well-attended “Death Becomes Us” True Crime convention in New York City in March 2019; numerous podcasts on true crime; and increasing numbers of novels, documentaries, and dramatic series depicting true crime. For example, the podcast Serial (2014) about the murder of Baltimore teenager Hae Min Lee recently became an HBO documentary series (2019). In the popular podcast My Favorite Murder, Karen Kilgariff and Georgia Hardstark tell each other true crime stories each week with comic interludes. Their tagline, “Stay sexy and don’t get murdered.”

Consistent with the true crime trend, in Family Murder: Pathologies of Love and Hate, Susan Hatters Friedman, MD, (and other authors on behalf of the Committee on Psychiatry and the Law of the Group for the Advancement of Psychiatry) uses a high-profile true crime vignette at the beginning of each chapter to illustrate its subject matter. In the introduction, Susan Smith, a notorious mother who drowned her two sons in a lake in 1994, is presented, and her story is used again in chapter six as an example of child murder by parents. The high-profile case of Lyle and Erik Menendez, which was recently made into a Law and Order miniseries (“Law and Order True Crime: The Menendez Murders”), was used to introduce parcide in chapter eight.

In addition to addressing compelling material, the comprehensive book on family murder serves as a guide to all psychiatrists—not only those who practice forensic psychiatry—on how to handle cases in each chapter. This book also would be relevant to general psychiatrists who may encounter patients with a history of violence or violent thoughts against family members, or patients who have been exposed to traumatic familial incidents. Topics covered include intimate partner homicide by men and women, feticide, neonaticide, fatal maltreatment and child abuse resulting in murder, child murder by parents, siblicide, parcide, intimate partner homicide in elderly populations, and familicide.

Each chapter is divided into multiple subsections—including the true crime introduction, background information, epidemiology, motivations, and multiple references—and addresses prevention, risk assessment, aftermath, and legal issues. All chapters offer guidance for the psychiatrist on the mentally ill offender and information on whether mental illness is a common contributor in the type of family murder. The statistics are often surprising. For example, when antisocial personality disorder is dropped, fewer than 5% of mentally ill parents have maltreated their children. The authors explain throughout the book that although a great deal of publicity surrounds the murder of family members, such murders are rare and, therefore, research and data in this area are limited.

I spoke to editor and author, Susan Hatters Friedman, MD, about the motivations for writing the book. She explained, “We sought to bring together comprehensive data about murder within the family, as well as real-life stories of this tragedy. We hope that the book is helpful to those completing evaluations after the fact—but, moreover, helpful to the ultimate goal of prevention.”

An interesting aspect of family murder described in the book is that there are often motivations of “love” as well as “hate,” as indicated in the subtitle, and the motivations are generally complex. For example, in the story described in chapter nine, an 88-year-old man had shot his 86-year-old wife in a hospital room and planned to shoot himself as well but was apprehended. He explained clearly to authorities his altruistic motive that his wife had been begging to die.

Family Murder is an in-depth guidebook that synthesizes the available research. It will be helpful for forensic psychiatrists who are evaluating someone who killed a family member or intimate partner and for general psychiatrists who are seeing patients for whom they are worried about the risk of family violence. The book will also be of interest to attorneys involved with these cases, as well as to the general public interested in true crime, since it is well written and concise. It will broaden the true crime fan’s knowledge about family murder, as the book situates the case vignette within what is known in the literature about that type of murder.

Dr Rosenbaum is a general and forensic psychiatrist in New York City and on faculty at New York Presbyterian–Cornell Weill and New York University Langone Medical Center.
Eating disorders, including anorexia nervosa, bulimia nervosa, binge eating disorder, and the newly defined avoidant-restrictive food intake disorder (ARFID), affect more than 5% of the population and are associated with high rates of morbidity and functional impairment. The etiology of these behavioral conditions is multifactorial and includes predisposing, precipitating and perpetuating factors.

Genetic vulnerability predisposes at-risk individuals to an eating disorder. Onset can be precipitated by dieting, puberty, exercise, or stressful life events; and as the disorder progresses physiological and neural changes arising from disordered eating and weight control behaviors feed forward to sustain the driven nature of these conditions. This two-part Special Report—beginning in this issue and continuing in the October issue—focuses on several topics ranging from recent research on the underlying neural mechanisms that maintain disordered eating in anorexia nervosa to guidelines on when to refer patients to higher levels of care as well as information on recognizing and treating ARFID.

What, when, and how we eat is controlled by the brain’s mesolimbic reward circuitry and by hormonal and neural gut—brain hunger and satiety signaling. Additionally, stress and sociocultural pressures shape the learning of eating behavior. Dysregulation in these controls of eating is no more apparent than in anorexia nervosa, where goal-directed dieting gradually takes on a compulsive nature and is no longer controlled by the homeostatic or hedonic drives to eat. As dietary restriction and weight control behaviors become progressively driven, affected individuals grow anxious about deviating from their eating and weight-control routines and increasingly unresponsive to escalating negative consequences of their behavior. Indeed, recent research implicates neural circuits relevant to addiction, anxiety disorders, and OCD in anorexia nervosa.

Two articles in this Special Report focus on how understanding the neurobiological and neurocognitive processes underlying anorexia nervosa inform new treatments and improve existing interventions for this challenging condition. Impairments in instrumental learning and a shift from goal-directed to habitual behavior, along with disturbances in approach-avoidance to food may contribute to the disorder’s tenacious persistence. Improved behavioral meal-based strategies that target fear of consuming calorie-dense foods, together with supportive and neurobiologically informed educational patient and family interventions, may help augment existing treatment approaches.

A related article focuses on interoception, the ability to sense and feel what’s going on inside the body and to integrate bodily sensation, cognitive processes, and emotions. Gut dysmotility and visceral hypersensitivity are frequent consequences of starvation and of binge-purge behaviors. Although largely reversible with normalization of eating behavior, altered somatic and visceral sensations may help sustain disordered eating and cognitions during the illness. Disturbances in interoception are also relevant to the heterogeneous group of patients subsumed under the new diagnostic category of ARFID, the focus of another article in this Special Report.

Two articles describe advances in the treatment of eating disorders and personalized care. Pharmacological interventions have only modest effects, and over 75% of clinical cases either go undetected or do not receive evidence-based care. The latter favors behaviorally based treatments that target normalizing eating and weight control behaviors. In patients who are underweight, starvation exacerbates cognitive and affective symptoms making weight restoration a treatment imperative.

Across diagnoses and interventions, early behavior change is consistently emerging as an important prognostic indicator. Manualized treatments with the strongest empirical support include family-based treatment (FBT) for adolescent anorexia nervosa and cognitive-behavioral therapy (CBT) for bulimia nervosa and binge eating disorder. With both treatments, shorter courses appear as effective as longer interventions. However, dissemination of these approaches has been slow among general psychiatrists and other mental health practitioners. One of the articles reviews reasons for the poor uptake of existing evidence-based treatments and presents emerging solutions that promise to facilitate training and improve implementation.

Finally, one of the articles spotlights the care of eating disorders in intensive treatment settings. Most specialty programs employ a structured behavioral protocol, supervised meals, multidisciplinary team support, and group therapies that emphasize recovery-oriented behavior change, and weight restoration for patients who are underweight.

For individuals with anorexia nervosa, body mass index at program discharge is correlated with risk of relapse. Approximately 50% of fully weight-restored patients achieve recovery. Whenever possible, meal-based nutritional rehabilitation is preferable to nasogastric feeding. Despite historical concerns regarding risk of refeeding syndrome, recent literature supports the safety and effectiveness of higher calorie diets and faster rates of weight gain on the order of 3 to 4 pounds a week as safe and effective when administered in the setting of close medical monitoring and prompt correction of hypophosphatemia and other glucose and electrolyte imbalances. Faster rates of weight gain are important as they help shorten both time in higher level of care treatment settings and the high cost of 24-hour daily specialty care.

We hope readers will find the articles in this Special Report on eating disorders a helpful update for formulating cases, talking to patients and improving management of these complex behavioral disorders. Eating disorders are common, making knowledge of diagnosis and management as well as basic familiarity with first-line interventions of importance for all psychiatrists. Treating eating disorders can feel challenging because patients are typically ambivalent about changing their behavior; however, it is also rewarding, as full recovery is possible even in the most chronically and severely ill patients.

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How Anxiety and Habits Contribute to Anorexia Nervosa

Teresa Rufin and Joanna Steinglass, MD

Anorexia nervosa (AN) is a severe and debilitating illness with one of the highest mortality rates of any psychiatric disorder. Epidemiologic studies show that AN affects males and females, children and adults, and individuals of all races and ethnicities, although some data suggest that it is most prevalent among white females.

AN is characterized by severe food restriction leading to an unhealthy low body weight, as well as body image distortion and intense fear of weight gain.

The illness course is often long, recovery is slow, and the rates of full recovery are low. Currently, treatments that emphasize behavioral change (with monitoring of eating and weight) are the most useful, with no one modality emerging as the treatment of choice. Medications have been generally disappointing, and none to date have been approved by the FDA for treatment of AN. A recent, large randomized controlled trial suggests a potential benefit of olanzapine for outpatients with AN.

Eating behavior in AN is, in many ways, impressively stereotyped. When food intake has been carefully measured through observation or laboratory studies, individuals with AN have been shown to limit caloric intake, and to specifically limit intake of fat. Dietary restriction occurs during acute illness and does not normalize with weight restoration. Food restriction can begin for a wide range of reasons beyond intent to lose weight. Some individuals, for example, may experience weight loss due to a medical illness, or after joining a new sports team.

Once restrictive eating behaviors are established, they become remarkably similar across individuals with AN: low-calorie diets with limited food variety and in particular, avoidance of fat. Eating is also associated with high anxiety and often accompanied by ritualized behaviors. Eating behavior studies underscore that the salient and central problem of AN is maladaptive eating.

Specialized behavioral inpatient units are highly successful in helping individuals with AN get renourished.

Unfortunately, relapse rates post-hospitalization are high. One challenge in treating AN is that maladaptive eating patterns persist even after acute treatment and have been shown to predict worse outcomes in the longer term. Individuals who were eating a wider variety of foods, and consuming food with higher energy density toward the end of their inpatient stay were more likely to be doing well one year after hospital discharge. Understanding how these patterns form and why they persist can provide insights into how to better treat this disorder.

Anxiety and AN

Links between anxiety disorders and AN have long been noted. Comorbid presentations are common, especially with OCD or social phobia. It is also common that an individual with AN had an antecedent anxiety disorder in childhood. Anxious personality traits including neuroticism, perfectionism, and harm avoidance are common among patients with AN. Underweight patients with AN report a range of anxious symptoms and score high on measures of anxiety. Significant amelioration of anxiety symptoms occurs with treatment, although weight-restored individuals endorse significantly more anxiety symptoms than healthy controls.

Mealtime anxiety, specifically, is very common and contributes to limited intake, which may be important in the persistence of illness. Neuroimaging studies have used fMRI to measure activity in neural circuits while patients with AN are passively viewing disorder-related stimuli (eg, food, bodies). These studies have shown activation of fear-related circuits that differs from healthy individuals. While these studies may support a role for fear circuitry in the persistence of AN, links with actual maladaptive behavior are not commonly tested.

High anxiety and the use of avoidance behaviors to manage anxiety lead to the proposal that eating-related anxiety is the cause of the persistence of illness, and it may be a useful treatment target. In the anxiety-centered approach to AN, avoidance behaviors and rituals around food are seen as akin to phobic behaviors, and rituals around eating are seen as akin to compulsions of OCD.

Habit and AN

The entrenched persistence of restrictive eating in AN has also led to consideration of the possibility that these behaviors have become habitual. Habits are defined as behaviors that are learned—not innate—and through repetition have become nearly automatic and highly resistant to change. Consistent with this model, restrictive eating is a learned behavior, and it is often described by patients as having been rewarding initially.

The rewards can be quite individualized: one person may have received compliments for weight loss that were rewarding, while another may find intrinsic reinforcement from a feeling of self-control. These experiences likely activate reward pathways in the brain (ie, ventral striatum, orbitofrontal cortex), which in turn support the continuation of food restriction. As restrictive eating continues, the goal-directed behaviors that were once reinforcing become more automatic. As behavior is repeated and entrained, it can become more tightly linked to the cues (external and internal) that stimulated the behavior and less linked to the previously rewarding outcome.

The process of habit formation is accompanied by a shift in neural correlates. Neural pathways implicated in habits include the dorsal striatum and the dorsolateral prefrontal cortex (dLPFC). Disturbances in the dLPFC and dorsal striatum are thought to underlie other psychiatric disorders characterized by repetitive, maladaptive behaviors, such as OCD and substance abuse.

For patients with AN, cues may include the expectation of food, changes in mood, or life stressors. In this habit-centered framework, the ritualistic, compulsive behaviors of the illness, such as cutting food into small pieces or body checking, have become linked with cues and are relatively independent of the outcome—and thereby more automatic. For example, body checking may have once served as a rewarding behavior for a patient who was monitoring her weight loss but has since become a nearly reflexive action occurring any time she eats.

In a first test of the role of habit in maladaptive eating behavior in AN, participants were asked to make choices about what food to have as a snack during fMRI scanning. Among individuals with AN, choice was associated ed with greater activity in the dorsal striatum compared with healthy controls. Activity in the dorsal striatum was correlated (ie, functionally connected) with a region in the dLPFC. These findings suggest that dorsal frontostriatal circuitry underlies maladaptive restrictive food choice in AN and provide support for the habit model.

Stress, habit, and anxiety in AN

Broadly speaking, stress may link anxiety and habit into one integrated model of AN. Stress induces alterations in various neurotransmitter systems (eg, dopamine, glutamate) and can facilitate habitual action patterns. Acutely ill patients with AN have been found to have chronically elevated cortisol levels that normalize with weight restoration. Chronic stress further strengthens habitual responses as den- dritic morphology in brain areas such as the nucleus accumbens and dorsolateral striatum is altered.

Moreover, starvation alters multiple hormonal systems that may influence learning and habit formation through neuromodulation. Combined, stress and starvation may have epigenetic effects that influence risk for AN or maintain the disorder.

Importance of behavior-based treatments

Successful treatment for AN may require both interruption of maladaptive habits (ie, excessive exercise and dietary restraint) combined with reduction in anxiety and avoidance behavior. These approaches differ in their mechanisms, but both emphasize a focus on behavior. Behavior therapy components are in many ways well established as useful in the treatment of eating disorders.

Family-based therapy (FBT), the first-line treatment for adolescents with AN, as well as specialized behavioral inpatient or day treatment programs for adolescents and adults, focus on behavioral elements. Outpatient psychotherapies such as cognitive behavioral and dialectic behavioral therapy for AN utilize behavior therapy as well. Yet, treatment outcomes remain disappointing. Habit and anxiety focused approaches may suggest new behavioral tools to improve treatment of AN.

Exposure therapy, the gold standard treatment for anxiety disorders, has...
been adapted for treatment of AN. Treatment emphasizes confronting—not avoiding—the feared stimulus and having in-session experience of disconfirming the feared outcome. These approaches have focused on eating-related stimuli or on body image (via mirror-exposure). Other potentially useful techniques may include increasing attention to extinguishing fears of risk foods in meal-based settings and body image therapy following weight restoration (as opposed to only during weight gain) as well as use of virtual reality environments. Most studies are small pilot approaches, but results have generally been encouraging.16 If maladaptive behaviors are habitual, however, then treatment needs to specifically address the cues that lead to the behavior (not the feared outcomes). In one pilot study, patients received an adjunctive intervention developed from habit-reversal therapy. The intervention identified cues for maladaptive behavior and focused on development of new actions in response to cues, as well as suppression of maladaptive routines. Compared with those who received supportive psychotherapy, the novel intervention was associated with decreased habit strength and decreased eating disorder symptoms.17

As neural mechanisms of maladaptive behavior are identified, new pathways for therapeutics emerge. Neuro-modulation with transcranial magnetic stimulation (TMS) may be used to directly target pathways implicated in fear learning and/or in habit formation. TMS of the ventromedial prefrontal cortex has shown promise in fear extinction and is beginning to be tested in AN.18,19 AN is a severe psychiatric disorder and patterns of restrictive eating have proven to be very entrenched, contributing to high rates of persistent illness. Current data suggest that these maladaptive eating patterns are related both to high anxiety and to habits. Neural mechanisms underlying this illness suggest that brain circuits related to fear and to reward learning may relate to illness. Behavioral interventions aimed at habit and anxiety reduction have shown promise, and their success provides further support toward future research in this area.

Ms Rufin is a graduate student in public health, and Dr Steinglass is Associate Professor of Clinical Psychiatry, Department of Psychiatry, Columbia University Irving Medical Center/New York State Psychiatric Institute, New York, NY. Ms Rufin reports no conflicts of interest; Dr Steinglass reports that she has financial interests in UpToDate, the NIMH. AWARENESS: the act of conceptually sensing, interpreting, and integrating information about the state of inner body systems.

Interoception in Eating Disorders: A Clinical Primer

More than two-thirds of patients with eating disorders also have comorbid mood and anxiety disorders.2 This suggests that the current system of symptom-based diagnosis incompletely identifies the underlying pathophysiological mechanisms driving these illnesses. This article considers how a transdiagnostic process called interoception may help to advance our understanding and treatment of eating disorders.

Overview of interoception
Consider for a moment the fact that every day our brains interpret sensory signals from the body in order to keep us out of harm’s way. The most common form of these signals relates to our ability to see predators looming in the distance, to hear them creeping up in the shadows, or to perhaps simply smell and avoid a poisonous piece of food. While the visual, auditory, and olfactory systems are clearly critical for survival, our brains are also constantly tracking a completely different world of ‘sensory signals—one.

INTEROCEPTIVE AWARENESS: the act of consciously sensing, interpreting, and integrating information about the state of inner body systems.

SPECIAL REPORT

INTEROCEPTIVE

the process by which the nervous system senses, interprets, and integrates cascades of these signals from within the body in order to maintain homeostasis.1

SIGNS OF INTENTIONALITY: unawareness and the inability to notice a change in your behavior, such as irritability? If you were alone, would you suffer in silence? How would you know whether you were hungry? Would you rely on others to notice a change in your behavior, such as irritability? If you were alone, would you suffer in silence? How would you survive? What if you could not detect the feeling of thirst? Sensing whether it is time to eat, drink, sleep, or excrete waste are dailylp rhythms that we engage in almost unconsciously. But not so for patients with eating disorders. Disrupted interoceptive awareness may negatively impact the mental health of individuals affected by eating disorders.

Interception in anorexia nervosa
Individuals with anorexia nervosa (AN) display a remarkable ability to ignore hunger cues and to maintain the body in a state of self-starvation, despite clamorous signaling from peripheral orexigenic hormones such as ghrelin.3 Contrary to usual settings, the corrective action of eating is experienced aversively by these patients, as evidenced by the fact that they report heightened fears at the prospect originating from within our bodies. Interoceptive sensory signals arising from the gastrointestinal, cardiovascular, respiratory, urogenital, hormonal, osmotic, gymnastic, and other systems are each in their own way critical to survival. What would happen if you were unable to sense when your blood sugar was low—how would you know whether you were hungry? Would you rely on others to notice a change in your behavior, such as irritability? If you were alone, would you suffer in silence? How would you survive? What if you could not detect the feeling of thirst? Sensing whether it is time to eat, drink, sleep, or excrete waste are daily rhythms that we engage in almost unconsciously. But not so for patients with eating disorders. Disrupted interoceptive awareness may negatively impact the mental health of individuals affected by eating disorders.
of eating a meal and assiduously avoid situations involving food. Individuals with AN show a dysfunctional processing of interoceptive signals during premeal periods, as evidenced by a heightened experience of sympathetic symptoms such as palpitations and dyspnea. They also show abnormal brain activity in areas important for interoceptive processing.

Acutely underweight patients show reduced functional connectivity in a brain network centered around the insular cortex, a region that is the primary cortical recipient of interoceptive signals relayed through the brainstem and thalamus. Weight restored patients exhibit greater insula activation in association with stomach sensations, but the opposite relationship happens in the amygdala, highlighting the potential role of negative affect in the body sensing process.

Following recovery these individuals exhibit hyperactivation in the insular cortex during the anticipation and resolution of restricted breathing loads (dyspnea) but, surprisingly, not during the loads themselves. Patients also abnormally classify taste stimuli—AN and bulimia nervosa patients have reduced insula responses to ingested glucose.

Taken together, these findings support the general hypothesis that patients with AN make erroneous inferences about internal body sensations in context-specific (eg, food-related) settings. These somatic errors may be key drivers of anxiety expression in the disorder. As clinicians, we can learn much about how these individuals perceive the world by studying the way their brains actively infer meaning about missing or ambiguously perceived interoceptive signals.

Abnormalities of interoceptive processing have been suggested at the neural level in bulimia nervosa, but methodological differences in the available studies limit firm conclusions. Even less is known about the effects of purging behaviors on interoception. Further tests that modulate gastrointestinal physiology and measure perceptual responses are needed to improve our understanding of the role of interoception in these disorders.

Developmental importance of interoception in eating disorders

The severe food aversion displayed by individuals with AN often develops during peripubertal periods, which suggests that a complex interplay between hormonal changes and stressful environments contributes to the expression of psychopathology. This has been characterized as a process of abnormal learning involving fear extinction neurocircuity, one that is driven by reduced or markedly fluctuating levels of estrogen. Even less is known about the role of interoceptive dysfunction in this process. From that standpoint, patient observations can sometimes shine a spotlight on areas worth investigating. A recent comment from a patient with an eating disorder during a diagnostic evaluation seems particularly informative.

...when anticipating a meal, individuals with AN tend to report false perceptions of interoceptive sensation, in the absence of any physiological changes.

Abnormalities of interoceptive processing have been suggested at the neural level in bulimia nervosa, but methodological differences in the available studies limit firm conclusions. Even less is known about the effects of purging behaviors on interoception. Further tests that modulate gastrointestinal physiology and measure perceptual responses are needed to improve our understanding of the role of interoception in these disorders.

Beyond food-associated discomfort, the fact that anxiety and suffocation fears were distinctly remembered as a key to the onset of her disorder emphasizes the importance of comorbid anxiety and leads to speculation whether signals from associated organ systems, such as the respiratory system, might have played a role in the development of her illness.

Assessing interoceptive awareness in eating disorders

In research settings the accuracy of interoceptive sensing is routinely tested; for example, by comparing a person’s actual heartbeat signals against a subjective report of them. Unfortunately, there are currently no clinically validated tests of interoceptive accuracy for gastrointestinal or any other interoceptive sensations. Clinicians can still assess interoceptive awareness in patients with eating disorders during diagnostic assessments by focusing on the constituent elements.

1. Ask patients to describe daily experiences of gastrointestinal, cardiovascular, and respiratory sensations. Are frequent bloating, cramming, palpitations, or dyspnea reported? How often do they focus their attention on these sensations? Is the attentional focus usually goal directed, as in frequent body scanning (top-down), or driven by the emergence of bodily signals (bottom-up)?

2. Where do these sensations occur? Do they incorrectly localize such sensations (eg, too diffusely, or in the wrong area)? Can they learn to correctly localize these sensations?

3. When do these sensations occur? Do they occur only during meal times, or during other notable changes in their external or internal environment? Examining the environmental settings under which these perceptions occur may help improve the understanding of context-specific factors.

4. How intensely do they perceive these sensations? Ask them to rate them on a scale of 0 to 10 (akin to rating the loudness of a speaker volume). Are there particular affective experiences associated with these sensations?

5. To what degree do they feel they are aware of their internal body sensations? Do they self-perceive the tendency to constantly focus on interoceptive signals? How does this attitude affect their eating disorder?

Psychometric assessments of interoceptive awareness are available. The first questionnaire developed to assess interoceptive awareness was the Interceptive Deficits subscale within the Eating Disorders Inventory, a self-report measure intended to assess eating disorder symptom severity. However, only two of the ten items actually assess interoception-related symptoms (eg, confusion about hunger, bloating after small meals), with the remainder of the items preferentially measuring alexithymia (eg, confusion about the emotion being felt).

The Multidimensional Assessment of Interoceptive Awareness Questionnaire captures a broader range of interoceptive experiences relevant for clinical settings. It has recently been validated in an eating disorders sample, with body trusting and self-regulation subscales showing the strongest correlations with clinical symptoms.

Treating dysfunctional interoceptive awareness in eating disorders

One approach that has been suggested to help weaken conditioned associations between interoceptive and environmental cues is interoceptive exposure therapy. Although originally developed for treatment of anxiety, it has been conceptually extended towards eating disorders. Using the process of extinction learning, patients are engaged in activities intended to elicit physiological sensations that are disorder-related, associated with negative affective states, and trigger maladaptive behavioral responses.

Patients may be repeatedly confronted with the sight and smell of foods, during which they closely attend to the associated sensations of hunger, salivation, or disgust. Over time, this weakens the conditioned association between the sensory signal and negative affective state, in hopes of reducing food avoidance behaviors.

Consumption of food can be incorporated into interoceptive exposure
therapy. One prominent clinician utilizes a chocolate frog as an exposure exercise, with a goal of successfully engaging the patient to examine, smell, and eventually eat this high-calorie food by the end of several sessions. Other potential interoceptive exposures involve gulping water (to elicit sensations of fullness or bloating), bouncing up and down (to elicit sensations of feeling body fat, or the movement of skin and muscles on the body), pushing the belly out (to elicit sensations of a tight belly), or sitting in a bean bag chair (to elicit sensations of sinking body weight).

An acceptance-based interoceptive exposure therapy has been recently described for children. Using playful cartoons to engage their curiosity about interoceptive sensations (eg, Gassy Gus, or Henry Heartbeat), the treatment trains children to increase food approach behaviors.17 The presence of these visceral illusions during the premeal state, a time marked by strong food-related feelings of fear and anxiety, suggests that closer attention to patients’ responses to environmental cues and behaviors leading up to a meal is warranted. It may be that the selection of maladaptive actions in response to these expectations (eg, self-starvation to avoid the actual sensing of visceral sensations) is an underlying core feature of eating disorders and represents a transdiagnostic target for clinical intervention.

**Conclusion**

We still have much to learn about the mechanisms driving food avoidance/approach behaviors in eating disorders. Studying interoception may provide new insights by characterizing how these individuals actively infer meaning about missing or ambiguously perceived interoceptive signals. For example, colleagues and I recently found that when anticipating a meal, individuals with AN tend to report false perceptions of interoceptive sensation, in the absence of any physiological changes.18 The presence of these visceral illusions during the premeal state, a time marked by strong food-related feelings of fear and anxiety, suggests that closer attention to patients’ responses to environmental cues and behaviors leading up to a meal is warranted.

**References**


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Eating disorders (EDs) affect individuals from every socioeconomic status, race, ethnicity, and gender, with approximately 10% of the population affected by an ED at some point in their lifetime.1 EDs are associated with high medical and psychiatric comorbidity, poor quality of life, and high mortality, and mortality from anorexia nervosa (AN) is the highest of all mental disorders.2 Fortunately, there are a number of evidence-based psychological treatment approaches for EDs. Three well-established treatments have emerged for patients who are medically and psychiatrically stable enough for outpatient care.1

Family-based treatment

The basic tenets of family-based treatment—often referred to as the Maudsly method—for adolescents with anorexia nervosa include3:

1. The family is not blamed as the cause of the illness.
2. The adolescent’s acceptance of family and parent involvement in therapy is crucially important; thus, parents are tasked with taking charge of weight gain in their malnourished child.
3. The entire family is an important part of treatment success.
4. Normal adolescent development is seen as having been interrupted by the illness.

The treatment typically consists of 10 to 20 sessions over the course of 6 to 12 months. Full nutrition is viewed as a critical first step toward recovery, and the early part of treatment is focused on the therapist coaching the parents to provide this nutrition by actively feeding their child.

Cognitive-behavioral therapy

Cognitive behavioral therapy (CBT) is a treatment for bulimia nervosa and binge eating disorder. According to the cognitive-behavioral theory of EDs, the over-evaluation and control of shape and weight is central to ED maintenance, with most of the other clinical features understood as directly resulting from this psychopathology, including extreme weight-control behavior and preoccupation with thoughts about eating, shape, and weight.

The core components of CBT are designed to be delivered in 20 sessions over 5 months. Key strategies include establishing control over eating with behavioral techniques, such as self-monitoring and establishing a regular pattern of eating and addressing maintaining factors (eg, control and over-evaluation of shape and weight, dietary restraint). In the enhanced version of CBT for EDs (CBT-E), modules can be added to address one or more external processes that may be maintaining the ED, including perfectionism, low self-esteem, and interpersonal problems.

Research findings suggest that guided self-help based on CBT can be effective in treating bulimia nervosa and binge eating disorder as well.3 Guided self-help can be defined as a psychological treatment where the patient takes home a standardized treatment, which is often written down in book form or available through some other media, and primarily works through it independently but also has the guidance of a therapist or coach. This guidance is primarily supportive or facilitative in nature and is meant to support the patient in working through the standardized treatment themselves.

The amount of contact in guided self-help is minimized relative to standard treatment approaches. It is acceptable to patients, highly cost-effective, and can be implemented successfully by a wide variety of individuals (eg, nurses, non-specialists with no formal clinical qualifications). For these reasons, as of 2017, the United Kingdom National Institute for Health and Care Excellence (NICE) guidelines for EDs recommend guided self-help CBT as the first-line treatment for adults with bulimia nervosa and binge eating disorder.4

Interpersonal psychotherapy

Interpersonal psychotherapy is another treatment for bulimia nervosa and binge eating disorder. It assumes that ED symptoms develop and are maintained in an interpersonal context. Specifically, interpersonal problems may contribute to negative affect and low self-esteem, which can in turn lead to the use of ED behaviors as a coping strategy.7 Engaging in ED behaviors can further intensify social difficulties, perpetuating the cycle. Interpersonal psychotherapy works to break this cycle by helping patients improve relationships and communication and resolve interpersonal issues.

Interpersonal psychotherapy typically includes 15 to 20 sessions over 4 to 5 months. During the early part of treatment, the onset and maintenance of the ED are linked to at least one of four identified problem areas (ie, interpersonal deficits, interpersonal role disputes, role transitions, grief) and interpersonal goals are developed. The focus of treatment then transitions to working towards these goals. During this process, the therapist helps the patient recognize the connections between improvement in ED symptoms and positive changes in interpersonal functioning.

The research-practice gap

Many international, evidence-based clinical treatment guidelines recommend use of these evidence-based psychological treatments for EDs. Despite the recommendations, when individuals with EDs receive care, it is frequently not evidence-based treatment. Referred to as the research-practice gap, this is the discrepancy between what is known about effective treatment and what is actually provided to patients who receive care. Indeed, the number of ED specialist clinicians who report adhering to evidence-based protocols is between 6% and 35%. Far more clinicians report using an eclectic mix of techniques derived from both evidence-based treatments and techniques with no evidence for efficacy.5 Furthermore, even when clinicians say they are using an evidence-based treatment for EDs, key elements may be omitted.6

“"We have powerful, evidence-based psychosocial interventions, but they are not widely available . . ."
The Research-Practice Gap

Continued from page 38

TRAIN-THE-TRAINER. Current approaches to training therapists to conduct new treatments typically consist of a 1- or 2-day workshop delivered by an expert; attendees are provided with a therapy manual. While workshops increase therapists’ knowledge, without further consultation their effect may be short-lived. Alternatively, there is a strong theoretical case for the “train-the-trainer” approach, which centers around an individual (the trainer) from a given setting (eg, community mental health center, college counseling center) who will be trained and will then train his or her colleagues. In addition, the trainer provides consultation as needed to anyone implementing the new treatment. In this way, the trainer becomes an internal coach and champion for the treatment.

This approach has been recommended as the most effective means of changing therapist behavior.11 The train-the-trainer approach also has the benefit of being more sustainable and cost-effective over time, as the trainer can continue to train new cohorts of therapists at relatively low cost. There is preliminary support for the usefulness of this method for guided self-help CBT.12 This approach is currently being tested as a method for training college counselors in interpersonal psychotherapy for EDs and depression.13

WEB-CENTERED TRAINING. Another method is web-centered training, which is scalable and low cost.

It has several key advantages:

1. Training can be offered to geographically dispersed trainees using minimal person-based resources.
2. The website can be accessed anytime, anywhere to effectively accommodate busy schedules.
3. It enables trainees to repeatedly review material, reinforcing learning.
4. The process can be customized to the trainee with quizzes, feedback, and refresher courses.
5. The website can be updated regularly, facilitating incorporation of new information.
6. Data collection on website usage can provide valuable information on the most accessed program features, informing refinement.

A comprehensive platform for training in CBT for EDs has been developed; findings indicate that the use of the platform may increase competence scores.14,15 Likewise, a comprehensive online training program in interpersonal psychotherapy has also been developed, including telephone-based simulation assessment for measurement of adherence and competence in the treatment, with testing currently underway.16

BEST-BUY INTERVENTIONS. When selecting an evidence-based treatment to disseminate, selection criteria should be based on best-buy interventions and include: efficacy, cost-effectiveness, clinical range, ease of training and learning, and mode of delivery.17 Transdiagnostic treatments may be considered best buys because they have the advantage of offering greater clinical range and thus more practicality, which may enhance adoption of the method by therapists. In that sense, interpersonal psychotherapy might be considered a best-buy intervention given its ability to not only address EDs but also a variety of other problems, including depression, anxiety, and PTSD.18

Cost-effectiveness is also a key consideration in defining a best buy. Family-based treatment might be considered a best buy given that it is cost effective compared with weight restoration via inpatient hospitalization. Likewise, guided self-help CBT has the advantage of being very easy to learn and deliver, even by inexperienced practitioners, making it very cost-effective.

ELECTRONIC SUPPORT TOOLS. Electronic support tools for therapists have the potential to enhance quality of care. First, checklists can help ensure important points are covered and aid in decision-making. Can also include routine outcome monitoring, including use of electronic measurement feedback systems.

HIGHER-LEVEL SUPPORT AND POLICY

• Greater likelihood of success in changing therapist’s behavior relative to relying on individual therapists to voluntarily receive training and modify their behavior

Conclusion and future directions

The establishment of several evidence-based psychological treatments for EDs, including family-based treatment, CBT, and interpersonal psychotherapy, represents an enormous advance. However, only a minority of patients with EDs who access care receive one of these treatments. To address the research-practice gap and ensure that more people obtain high-quality, evidence-based care, the use of novel approaches are required.

What will be most effective in terms of meaningfully addressing the research-practice gap is higher-level support and policy, which has the greatest likelihood of generating widespread change. It is important to work with policy makers to develop research questions that will answer important policy-related questions. Such an approach may dramatically increase access to evidence-based care for patients with EDs.

There is an enormous treatment gap in the field of EDs, whereby the vast majority of patients with EDs (≥ 80%) receive no clinical care whatsoever.19 Moving forward, in addition to continuing to improve the quality of treatment for the minority of individuals with EDs who receive services, increased attention needs to be devoted

TABLE. Key characteristics of approaches for addressing the research-practice gap

| TRAIN-THE-TRAINER | • Expert training is provided to a single therapist | • Trainer goes on to train other therapists at his/her organization | • Trainer acts as an internal coach and champion |
| WEB-CENTERED TRAINING | • Using the internet to train therapists | • Lower in cost and more scalable than traditional methods |
| BEST-BUY INTERVENTIONS | • Implementation of interventions selected based on their efficacy, cost-effectiveness, clinical range, ease of training and learning, and mode of delivery | • Originally conceived as an economic tool to help countries select among evidence-based strategies to achieve a given amount of change |
| ELECTRONIC SUPPORT TOOLS | • Have the potential to enhance quality of care | • Checklists can help ensure important points are covered and aid in decision-making |
| • Can also include routine outcome monitoring, including use of electronic measurement feedback systems |
| HIGHER-LEVEL SUPPORT AND POLICY | • Greater likelihood of success in changing therapist’s behavior relative to relying on individual therapists to voluntarily receive training and modify their behavior |

For evidence-based care to dramatically increase, higher-level support is required. Improving Access to Psychological Therapies (IAPT) is a systematic way of organizing the delivery of evidence-based psychological treatment, according to the NICE guidelines, within England’s National Health Service. IAPT services are characterized by use of evidence-based treatments, routine outcome monitoring, and regular and outcomes-focused supervision.20 Routine outcome monitoring not only provides the patient and therapist with valuable information on symptom improvement, but it also provides information on whether this is a cost-effective approach. In the US, the Veterans Health Administration (VHA) is actively implementing a national initiative to disseminate and implement evidence-based treatments.21 IAPT and the VHA models involve centralized control of money from the top and their implementation is mandated. Such initiatives have a much greater likelihood of success in changing therapist behavior relative to relying on individual therapists to voluntarily receive training and modify their behavior.

CONTINUED ON PAGE 50

EATING DISORDERS: PART 1

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**PSYCHOSOMATICS**

**How Catastrophe Can Change Personality**

**Why EPCACE Is a Clinically Useful Diagnosis**

Gen Tanaka, MD, Hansen Tang, Omar Sultan Haque, MD, PhD, and Harold J. Bursztajn, MD

Any psychiatric diagnosis has the potential for empowering the clinician to treat the patient’s suffering as well as inspiring the patient to participate in an effective treatment. Alas, diagnosis also has the potential for stigmatization and dehumanization. Whereas diagnoses of personality disorder all too often have been used to stigmatize patients, the rush to eliminate Enduring Personality Change After Catastrophic Experience (EPCACE) from the International Statistical Classification of Diseases, Revision 11 (ICD-11) is foreseeable an instance in which patients vulnerable to aloneness will be less likely to receive effective treatment and thus will become even more voiceless, further disempow-erment and thus will become even less likely to receive effective treatment. Alas, the underutilization of EPCACE is a loss for a significant proportion of patients who might otherwise have united as a treatment community. This loss is compounded by the fact that aloneness is often seen in the transgenerational transmission of EPCACE-related suffering. Group therapy is therefore a vital modality in EPCACE treatment across generations and in fostering the transgenerational transmission of resilience.

A follow-up study of the validity and utility of EPCACE in 2008 by Beltran attempted to redefine the broad aspects of the diagnosis and identify the key criteria that described a person with EPCACE. Twenty-four mental health clinicians who worked with patients who had experienced war and sexual assault as well as recently displaced refugees provided valuable feedback. Not only were the key attributes of “A hostile or mistrustful attitude toward the world, social withdrawal, feelings of emptiness or hopelessness, a chronic feeling of being ‘on edge,’ as if constantly threatened, and estrangement” identified, but mental health practitioners felt significant features were excluded from EPCACE’s operational definition. These include “somatization, self-injurious/self-damaging behaviors, sexual dysfunction, and enduring guilt,” which if included would differentiate EPCACE from complex PTSD and strengthen the operational validity of the diagnosis. Since then, no changes to criteria or follow-up studies have been conducted to improve the utility of EPCACE.

Research into EPCACE has been limited, as manifestations of the core symptoms can often differ depending on viewpoints and type of trauma. A core feature of EPCACE such as “a hostile or mistrustful attitude toward the world can be operationally expressed by multiple symptoms such as anger, aggression, and other count- less variations.”

Holocaust survivors who were identified as “feeling as if
the Holocaust experience was continuing” were more likely to suffer symptoms of mental disorder, whereas those who avoided the traumatic memories altogether had a higher mortality rate due to illness.44 Patients with a diagnosis of EPCACE may isolate themselves not only from their communities, but also from proper mental health care.

**Alternatives to inclusion of EPCACE as a distinct diagnosis**

Critics of the inclusion of EPCACE in diagnostic taxonomy claim that it lacks specificity and is insufficiently utilized. To address these concerns, Maercker and colleagues proposed to reconceive EPCACE as part of cPTSD in ICD-11. Following this recommendation, the World Health Organization trauma team eliminated the diagnosis of EPCACE. cPTSD incorporates patients with personality changes as a result of exposure to single or multiple traumatic experiences, as long as the requirement of three core features of PTSD is met; these core features include changes in affect, self-concept, and relational function.

Alas, modifying the diagnostic criteria for cPTSD to consolidate EPCACE and other trauma-related disorders may also lead to mislabeling and downgrading the seriousness of personality changes, as well as overlooking potentially transgenerational personality changes. Because different experiences may produce different neurological and behavioral effects, it would be unwise to disregard the type of event and its impact on affect.

A later study noted a more specific set of criteria that must be met, as well as additional symptoms such as changes to somatization, self-injurious/self-damaging behaviors, and sexual dysfunction that would largely be left out of the criteria for cPTSD. The current criteria for cPTSD—which encompass the majority of EPCACE cases tested by Keeley and colleagues—faced diagnostic issues when practitioners became aware of the origin of the trauma.

Another argument against the diagnostic inclusion of EPCACE is symptom overlap between EPCACE and cPTSD. While there is a spectrum of post-traumatic disorders, with overlap among diagnostic categories, the presence of such similarities does not invalidate the clinical usefulness of an EPCACE-inclusive categorical approach in the initial process of clinical reasoning, differential diagnosis, treatment planning, and prognosis. Therefore, future ICD workgroups should reconsider EPCACE’s inclusion into cPTSD, given the weight mental health professionals place on traumatic origin, and restore EPCACE as a distinct diagnosis.

The American Psychiatric Association has opted for a more conservative route in DSM-5 by incorporating elements of cPTSD and EPCACE into the diagnosis of PTSD. DSM-IV had largely suffered from “poor interrater reliability of personality disorder diagnoses, poor stability over time, poor discriminant validity, and poor general coverage of personality disorder as well as poor clinical utility.” DSM-5 requires that adult patients be evaluated for stress disorders meet eight symptomatic criteria following exposure to trauma. Galatzer-Levy and Bryant found that the current diagnosis for PTSD could arise from 636,120 unique combinations of the eight criteria listed in the newly formulated definition. With so many combinations, PTSD has been utilized as an all-encompassing definition that lacks the specificity needed to adequately diagnose trauma. The diagnosis of trauma-related disorder should not be done on a one-size-fits-all basis, but rather should consider the elements of trauma and its disparate effects on individuals.

**Why EPCACE should be reborn as a distinct diagnosis**

As it currently stands, EPCACE has lost its core values in the newly revised ICD-11 and the previously published DSM-5. Given that EPCACE is marked by hostile attitudes toward society, withdrawal, emptiness, and hopelessness as well as constant vigilance and estrangement, the salient characteristic of the disorder is the sense of aloneness that leads to massive social disconnection. EPCACE has significant features in common with the kinds of compounding trauma seen in autism spectrum disorder or adolescent-onset psychosis as a person becomes isolated and marginalized. With EPCACE, patients suffer a loss of community and trust with the inside world. With the loss of community, as in the Holocaust, there is an ever-greater risk of the transgenerational transmission of trauma and far fewer transgenerational resources for resilience such as loving grandparents or an extended healthy family.

EPCACE should be a stand-alone diagnosis rather than a formulation because diagnoses are heuristics for formulations, which guide prognosis and treatment planning. Also, if diagnoses are missing key ideas, those will also be missing in formulations. Aloneness and vulnerability are distinct factors characteristic of EPCACE that are coherent only at the diagnostic level. Moreover, with catastrophic experiences the life cycle and transgenerational dimensions of trauma and resilience are more likely to be central.

The majority of mental health clinicians in active practice or completing graduate education will utilize either DSM-5 or ICD-11. When Evans and colleagues surveyed a global sample of psychologists, they noted that 78% of respondents opted for a diagnosis that is flexible enough to account for cultural differences. Severity of a diagnosis was highly rated as a goal of clinical care, as 88% of the respondents believed that it should take the form either of a subtype based on severity or degree of functional impairment or of a separate diagnosis.

Further research has linked trauma to quantifiable changes in personality. In a comparison of late-onset personality pathology due to wartime trauma with prior personality disorders, 24.3% of patients had a personality disorder develop only after exposure to catastrophic events. When compared with those who had preexisting personality disorders, those with late-onset personality pathology had a three-fold higher rate of PTSD symptoms. Moreover, there were higher rates of suicidal ideation and self-reported emotional distress compared with persons with pre-trauma pathology.

Additional research has shown not only physical changes to the brain but also transgenerational effects that pass from parent to offspring.21 Such a link between catastrophic experiences and personality necessitates the use of integrative criteria such as EPCACE, which will serve the interests of patients and empower clinicians in making treatment decisions.

Self-help networks for EPCACE patients not only ease personal growth but also offer a safe communal space for patient empowerment. For example, since the aftermath of World War II, displaced and persecuted populations have found themselves unified and united by their shared experiences. Illustrative are reports of suffering experienced throughout Europe by survivors of massive psychic trauma with loss of their nurturing emotional milieu. Having the capacity to identify such traumatized populations from various countries and backgrounds and to unite them under a self-help support network enables survivors to create community for one another and foster therapeutic approaches which, via an empowering community, seek transgenerationally to treat the transmission of trauma and encourage the transmission of resilience.

Aloneness, along with helplessness about being alone and feeling humiliated, has increasingly been found to be a major risk factor across the illness spectrum. Aloneness post-trauma and in the midst of grief, to which persons who suffer from EPCACE are highly vulnerable, can reasonably be expected to compound this risk factor. Therefore, the diagnosis of EPCACE can be an important step toward remediation rather than exacerbation of aloneness, helplessness, and humiliation that, in a vicious cycle, can lead to further isolation.

**Conclusion**

To avoid the misuse of EPCACE, it is vital to be aware that some survivors of catastrophic experiences in which terror involves dehumanization, degradation, and humiliation may therefore experience a heightened sensitivity to helplessness and humiliation. Receiving any psychiatric diagnosis is humiliating; therefore, patients frequently avoid seeking clinically based help. However, a newly empowered population brought together by that very catastrophic experience can provide solace, rebuild self-esteem, and relieve ongoing collective suffering.

All too often, both the fragility of aging and disturbing news events bring home to EPCACE sufferers disturbing reminders of catastrophic trauma. When applied with care, EPCACE as a diagnosis is not only helpful in clinical formulation and treatment planning but also has the potential to support the creation of healing communities for life-cycle stressors and losses. EPCACE-informed development of additional treatment modalities, such as group bereavement therapy and support groups outside of the clinical context that are focused on supporting survivors’ agency, empowerment, self-respect, connectedness, and creativity, has the potential to reduce post-catastrophic isolation, demoralization, and suffering.

CONTINUED ON PAGE 50
Green Spaces

When the green woods loud with the voice of joy,
And the dimpling stream runs laughing by;
When the air does laugh with our merry wit,
And the green hill laughs with the noise of it.

William Blake was onto something in his “Laughing Song” poem. We need green spaces. Not only are they pleasant to look at, but these spaces are also healing. Almost anyone who has spent substantial time in a forest, up a mountain, or along a river recognizes that this is healing.

Nature provides both physical and psychological benefits. Studies have shown improved healing in hospitals with green spaces outside windows rather than brick walls and decreased anxiety and increased workplace satisfaction in offices with plants and/or views of nature.1,2

How does this healing through exposure to nature occur? A variety of possible mechanisms have been proposed, from improved air quality to increased physical activity and enhanced social integration. Ming Kuo, PhD,3 has studied how green spaces affect humans and has postulated that there may be at least one common pathway toward wellness acting as a buffer. Ming Kuo is Associate Professor at the Canadian Climate Psychiatry Alliance and the Canadian Climate Psychiatry Alliance. Dr Young reports no conflicts of interest concerning the subject matter of this article.

Pattern of negative, self-referential thoughts and emotions. The subgenual prefrontal cortex has demonstrated increased activity during rumination (in healthy and depressed individuals) and has been found to have increased connectivity to the default mode network in those with depression. In a study by Bratman and colleagues,4 walking in green spaces as compared with walking in urban spaces was associated with reduced activity in the subgenual prefrontal cortex, accompanied by a decrease in rumination.

As of 2017, approximately 82% of the US population lives in urban areas.5 Increased urbanization has been associated with a rise in a variety of mental illnesses, although the etiology is not fully understood and the mechanisms are likely diverse.

Greater exposure to green spaces may help improve mental and physical well-being. Physicians have begun to prescribe time in nature to their patients—I encourage my patients to get outside daily and into nature. Some of the innovative programs that exist to “prescribe” green spaces are available at: https://prescriptiontrails.org/ and http://www.gwaparkrx.com/.

Urban green spaces can help mitigate the effects of climate change. Cities account for much of the carbon dioxide emissions on our planet. Green spaces sequester carbon in plants, soil, and water. They also mitigate the effects of urban heat islands, which develop where buildings, parking lots, roads, and other infrastructures create an urban heat island effect. As of 2017, approximately 82% of the US population lives in urban areas. Increased urbanization has been associated with a rise in a variety of mental illnesses, although the etiology is not fully understood and the mechanisms are likely diverse.

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References
The central nervous system (CNS) complications of human immunodeficiency virus (HIV) infection triggered directly by the virus and not by an opportunistic pathogen were recognized early in the course of this epidemic. The initial descriptions were primarily of a severe progressive illness termed the AIDS Dementia Complex. Several decades later these neurological complications persist with a different name and mostly in a milder form, which nonetheless can still be disabling.

HIV-infected individuals beginning combination antiretroviral therapy (cART) in seven underdeveloped countries has established neurodiagnostic criteria and a similar worldwide prevalence of HAND. This is based upon abnormal neuropsychologic test performance and an effort to diagnose HAND with tests applicable to re-evaluation of their patient for contraindications or dangers of use. Medical professionals should not utilize the procedures, products, or diagnosis techniques discussed during this activity without first evaluating the patient’s needs. They will be discussing off-label or investigational uses (any uses not approved by the FDA) of products or devices. CME Outfitters, LLC, and the faculty do not endorse the use of any product outside of the FDA-labeled indications. Medical professionals should not utilize the procedures, products, or diagnosis techniques discussed during this activity without evaluation of their patient for contraindications or dangers of use.

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Since the mid-1990s, HIV-associated dementia has been relatively uncommon in areas where cART is widely available, such as the US. HIV-associated dementia was described soon after the association of HIV with the syndrome of AIDS, in the 1980s. In those earlier years of the HIV epidemic when treatment was mostly ineffectual, approximately 20% to 30% of individuals had HIV-associated dementia, or AIDS Dementia Complex as it was then known.4

HIV-associated dementia is a severe dementing illness that begins with disturbances of memory and cognition that affect daily living and progresses to psychomotor retardation, inability to recognize close friends or relatives, and eventual immobility. The psychomotor symptoms point to its subcortical etiology, consistent with the neuropathology of HIV-associated dementia. At its height (prior to cART) it was so widely recognized that it was immortalized in the second movement of Symphony Number 1 (1988-1989) by John Corigliano, who

Despite the dramatic decrease in the prevalence of HIV-associated dementia (to about 2% with cART) the less severe but nonetheless disabling form, mild neurocognitive disorder, affects approximately 15% of virally suppressed HIV-positive individuals today.6 Some studies suggest that up to 70% of patients with HAND who are receiving cART remain stable (at least over several years), while about 15% improve and an equal percentage further deteriorate.4 An unanswered question is how HAND prevalence will change over decades of life experience by many individuals receiving cART.

**Evolving brain pathology in HAND**

In addition to CD4-positive lymphocytes, productive HIV infection in the CNS is principally restricted to macrophages and microglial cells, which are principally derived from mesodermal bone marrow and yolk sac precursors, respectively. HIV infection of the brain occurs within days of systemic infection, and levels of HIV RNA in the cerebrospinal fluid (CSF) correlate with the severity of HAND in individuals who are naive to antiretroviral therapy.7

Studies of CSF derived from patients within days or weeks of HIV infection suggest a “Trojan horse” mechanism of entry of HIV-infected CD4-positive T lymphocytes into the brain and subsequent adaptation of the virus to infect macrophages and microglia.8 This can establish viral reservoirs that are at least partially inaccessible to antiretroviral therapy. In patients who receive suppressive cART (ie, with undetectable plasma virus levels), the presence and severity of HAND correlate with certain biomarkers of inflammation and neuronal injury that are likely initiated and amplified by HIV infection of macrophages and microglia and immune activation of non-infected cells.9

There is some trafficking between the systemic cellular precursors of macrophages and the brain, and they are often prominent in the perivascular spaces; less so for microglia that are parenchymal and long-lived, allowing for persistence of HIV in the CNS as well as persistence of neuroinflammation. Macrophages and microglia are the only cells in the brain that have the full complement of HIV surface receptors (ie, CD4 and CCR5); other brain cells may express CXCR4 (another HIV receptor) but not in conjunction with CD4, thereby preventing efficient entry of HIV. Brain autopsy studies have identified perivascular macrophages and parenchymal microglia as a major CNS site of productive HIV replication and inflammation, although astrocytes (up to approximately 15% infection rate) can also contain HIV genomes.10

The pathological hallmark of HIV-associated dementia is the postmortem presence of multinucleated giant cells that contain viral proteins and RNA/DNA, and are thought to be derived from the fusion of infected cells.7 The presence of multinucleated giant cells in autopsy specimens probably indicates that these fused cells live for a period that is likely to be more than a few hours; specific determination of the timeframe is probably impossible with current technology.

It is thought that this long antemortem period of HIV replication within these giant cells drives the pathogenesis of HAND, primarily through elaboration of pro-inflammatory and otherwise toxic signaling cascades in infected cells. Some non-infected cells may also be activated by the presence of multinucleated giant cells. These cells are associated with severe neuronal injury and death, for which several cell death pathways, including apoptosis and necrosis, have been implicated. However, in the era of cART some individuals with HAND have no discernible neuropathological abnormalities despite having functionally significant neurocognitive impairment.

### Pathophysiology of HAND

The pathophysiology of HAND in the pre- and post-cART eras is certainly multifactorial, involving effects of virus replication, residual brain injury prior to initiating cART, and variably expressed neurotoxicity cascades (Figure). Excluding multiple comorbid risk factors for brain injury that affect many subjects with HAND, its expression is likely to depend partly on the presence of varying degrees of, and intermittent expression of, neuroinflammation and oxidative stress, which are reduced but not eliminated by cART suppression of HIV replication.11

Direct neurotoxic effects of cART on brain cells have also been implicated. In addition, early brain injury secondary to disruption of the blood-brain barrier within the first weeks after infection or residual damage from long-standing HIV infection before the initiation of cART (ie, legacy effect in some individuals) may result in an irreversible level of persistent cognitive impairment.12

Inflammatory and neurotoxic cascades mediated by macrophages, microglia, and astrocytes have received the most attention. In addition to detection of HIV in macrophages and microglia in situ, virus-specific material (either DNA or proteins) has also been detected in other CNS cells, particularly astrocytes. However, in most cases the infection is not active (ie, not productive viral progeny). This could be a sampling error given the large number of astrocytes in the human brain and the possibility that only a small proportion could be productively infected at any one time. Whether this astrocytic infection is pathophysiologically important, whether or not it induces neuroinflammation, and whether these cells can serve as a long-term reservoir for infection remains possible, but it has never been incontrovertibly proven and has not been the focus of major treatment efforts.

Although analysis of CSF HIV levels in patients receiving cART indicates that suppression of HIV replication can be achieved within the CNS, surprisingly high rates of HIV escape from suppressive cART occur (ie, “blipping” of HIV replication). This is determined by sequential sampling of CSF and episodic detection of both HIV RNA and markers of immune activation of macrophages and microglia in individuals felt to be in a state of HIV suppression. Studies suggest transient HIV replication occurs in approximately 5% to 20% of patients.16

### The prevalence of HAND has not decreased after the widespread institution of cART; however, the distribution by severity has changed.

Brain macrophages and microglia are thought to contribute to the development of brain injury and dysfunction in HAND through several mechanisms. Microglia are involved in many neurodevelopmental functions, such as synaptic/dendritic trimming, and are implicated in other neurological conditions. Perivascular macrophages, on the other hand, are not thought to be involved in neuronal trimming. Rather, they form part of the immune mechanisms of the brain.

#### Table 1. Frascati Criteria for the Diagnosis of HIV-Associated Neurocognitive Disorder (HAND)1

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>Asymptomatic neurocognitive impairment</td>
<td>One standard deviation or more below the mean in two cognitive domains in standard neuropsychological tests but without any symptoms of dysfunction; cognitive domains usually tested are attention, executive function, learning, memory, processing speed, motor skills</td>
</tr>
<tr>
<td>Mild neurocognitive disorder</td>
<td>One standard deviation or more below the mean in two cognitive domains in neuropsychological tests with mild symptoms or functional impairment (eg, difficulty with employment, driving)</td>
</tr>
<tr>
<td>HIV-associated dementia</td>
<td>Two standard deviations or more below the mean in two cognitive domains in neuropsychological tests with severe impairment in activities of daily living</td>
</tr>
</tbody>
</table>

Note: HAND can only be diagnosed when other potential causes of neurological impairment, such as infections, metabolic abnormalities, or malignancy, have been ruled out.
A unifying hypothesis for the translation of a microglia/macrophage infection into a cognitive illness suggests that it is the secretion of cytokines and other immune mediators from these cells that affects neuronal function and perhaps survival. This hypothesis is consistent with the role that these cells are thought to play in other neurological conditions such as Alzheimer disease and stroke. It is also possible that infection of microglia interferes with their role in synaptic trimming or other intrinsic functions of these cells.

An alternative hypothesis is that some HIV proteins can themselves be toxic to neurons by binding at their surface and interfering with normal functions, possibly by excitatory mechanisms. In this scenario, secretion from infected macrophages or microglia is responsible for HAND abnormalities. The larger of the two viral glycoproteins (gp120) is the most effective target for reduction of the viral burden and infected macrophages/microglia is the most effective target for treatment. Whether free gp120 is present in the brain at concentrations consistent with those that mediate toxic effects, the attention of a psychiatrist.

The prevalence of HAND has not decreased after the widespread institution of cART; however, the distribution by severity has changed. For example, in patients with well-controlled HIV, the prevalence of HAND has decreased from 1980s. The additional risks and adverse effects of methamphetamine use, including increased HIV acquisition rates, are particularly relevant for men who have sex with men, for which risk reduction strategies are being evaluated. Besides behavioral risk effects, methamphetamine has neuropathological effects such as damage to dopaminergic neurons and enhancement of HIV infection of macrophages; each can contribute to the worsening of HAND.

An HIV-positive patient who presents with any neurological deterioration, particularly involving cognition, must have a detailed medical history assessment and a battery of diagnostic tests, chief among these are brain imaging and CSF analysis. Because many patients on cART are well-controlled virologically, free of opportunistic infections, and growing older, conditions associated with aging such as Alzheimer disease may confuse the clinical picture.

Substances of abuse and methamphetamine in particular are a major contributing risk factor for cognitive dysfunction in patients with HIV with or without underlying HAND. The additional risks and adverse effects of methamphetamine use, including increased HIV acquisition rates, are particularly relevant for men who have sex with men, for which risk reduction strategies are being evaluated. Besides behavioral risk effects, methamphetamine has neuropathological effects such as damage to dopaminergic neurons and enhancement of HIV infection of macrophages; each can contribute to the worsening of HAND.

An HIV-positive patient who presents with any neurological deterioration, particularly involving cognition, must have a detailed medical history assessment and a battery of diagnostic tests, chief among these are brain imaging and CSF analysis. Because many patients on cART are well-controlled virologically, free of opportunistic infections, and growing older, conditions associated with aging such as Alzheimer disease may confuse the clinical picture.

The prevalence of HAND has not decreased after the widespread institution of cART; however, the distribution by severity has changed. For example, in patients with well-controlled HIV, the prevalence of HAND has decreased from 1980s. The additional risks and adverse effects of methamphetamine use, including increased HIV acquisition rates, are particularly relevant for men who have sex with men, for which risk reduction strategies are being evaluated. Besides behavioral risk effects, methamphetamine has neuropathological effects such as damage to dopaminergic neurons and enhancement of HIV infection of macrophages; each can contribute to the worsening of HAND.

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rigorous assessment of abnormalities by using biomarkers. In reality, it is the prevalence of two related but not identical entities that has remained constant throughout the HIV pandemic.

HIV-associated dementia, the severe form of HAND, occurs primarily in the setting of low CD4 counts (<200 cells/μL), typically in individuals who are untreated. Initial abnormalities are difficulty with memory, inability to function effectively at work particularly in highly demanding pro-
cessions, and eventually psychomotor retardation. The latter is characterized by slowness of move-
ment and extrapyramidal signs.

In severe cases, T2-weighted brain MRI may demonstrate bilateral non-enhancing white matter abnormalities involving virtually both hemispheres. The CSF may have an elevated protein and detectable viral RNA, with a variable degree of lymphocytic pleocytosis. There are also several potential CSF markers such as neopterin and low molecular weight neurofilament chain (neurofilament light chain), each of whose levels correlate with dysfunction.26

Neopterin, a marker of inflammation, can also be present even in asymptomatic patients with ev-
idence of viral replication within the CNS. Neuro-
psychological testing is the gold standard for the
diagnosis of cognitive problems. Typical testing for HAND includes analysis in six functional cogni-
tive domains (Table 1). While

neuropsychological testing is essential for individuals whose diagnosis is in doubt and for
formal epidemiological or biological marker stud-
ies, this testing is generally unnecessary in indi-
viduals with HIV-associated dementia. The diag-
nosis can be clinically based on a history of difficulties with activities of daily living and by
performance using less complex testing such as the
Montreal Cognitive Assessment (MoCA).27 In
the current era of cART, many clinicians believe that the symptoms of HIV-associated dementia are more commonly cortical (impairment of memory, difficulty with executive function) than the subcortical dementia with motor symptoms that char-
acterized the initial descriptions of HIV-associated dementia. Therefore, tests that do not include motor components, such as the MoCA, are ade-
quate for HIV-associated dementia diagnosis.

Combination antiretroviral therapy

The principal goal of treatment of HAND is the systemic suppression of HIV; the number of cART drugs currently available is robust enough to pre-
clude any detailed discussion of the components of cART in this short review. However, one area that has received a lot of attention is the impor-
tance of CNS penetration by cARTs, quantified by a CSF penetration effectiveness score.28 With the exception of HIV-associated dementia, where CNS penetration may be important for rapid revers-
ald, most clinicians opt to treat for maximum sys-
temic suppression of viral RNA rather than for
CNS concentration.

Moreover, there is little evidence that antiretro-
viral drugs with enhanced CNS penetration are better as treatment for asymptomatic neurocognitive impairment or mild neurocognitive disorder, although this may be due to the difficulty in con-
ducting accurate studies over a relatively long pe-

Evidence of early blood-brain barrier involvement after initial HIV infection indicates that co-administration of neuroprotective adjunctive therapy is needed.

period of time. In general, clinicians who are con-
cerned about neurological symptoms avoid efavirenz, which is known to have neuropsychi-
atrie adverse effects.

The potential CNS toxicity of other antiretrovi-
ral drugs has also been proposed as a cause for persistent asymptomatic neurocognitive impair-
ment or mild neurocognitive disorder in otherwise
effectively treated individuals and such toxicity can be demonstrated in vitro. However, because of the likely subtlety of such toxicity and the complexity of many antiretroviral regimens, it has been difficult to tease this out.

What is clearer is that in a subset of individuals (~5% to 20%), there is persistent presence of viral RNA in the CSF in spite of good control in the plasma. Typically, the threshold for consideration of discordance is a greater than 0.5 log higher con-
centration in the CSF than in the plasma. This CSF viremia may arise from endogenous cells such as macrophages or microglia or be the result of the individual replication of infected T cell clones within the neuraxis.29 In either case the CSF virus does not necessarily result in neurocognitive ab-
normalities; the CSF virus has been noted in asymptomatic individuals as well as in some with
neurological worsening. Where appropriate—par-
ticularly in symptomatic patients—the usual
course of action is to alter the specific cART to one that is more effective, either empirically or guided by genotypic analysis of the CSF viral genome.

Adjuvant therapies

A relatively rare but perplexing syndrome can also occur in some patients with low viral (plasma and CSF) RNA levels who develop signs of brain white matter damage. Brain MRI for these indi-

viduals demonstrates white matter lesions. When biopsied the brain tissue is infiltrated with CD8-positive lymphocytes. CD8 encephalitis is consid-
ered part of a spectrum of CD8 infiltrative conditions that can involve the lungs and other or-
gans in individuals with HIV infection.30 It has also been associated with cART-resistant HIV strains. This entity responds to brief treatment with steroids sometimes coupled with modifica-
tion of the cART regimen.

Candidate adjuvant neuroprotective therapies have been used only with cohorts of HIV-infected individuals with symptomatic HAND (mild neu-
roognitive disorder and/or HIV-associated de-
mementia) with limited evidence of beneficial ef-
effects.16 However, because of emerging evidence of early (days to weeks) blood-brain barrier involve-
ment and brain injury after initial HIV infection, co-administration of a neuroprotective adjunctive therapy at the time of cART initiation should be investigated.

Other considerations

The excellent systemic response to cART has re-
sulted in a marked and welcome increase in lifespan for individuals living with HIV.31 Researchers have raised the possibility that asymptomatic or mildly symptomatic forms of HAND, such as asymptom-
atic neurocognitive impairment and mild neurocog-
nitive disorder, will convert to more significant problems in combination with the effects of aging on the CNS. For example, given its predominantly cortical pathophysiology in the era of cART, HAND must be differentiated from other disorders of cognition that are associated with aging, particu-
larly in patients aged older than 70 years, and in those whose treatment with cART may have been initiated later in the course of infection.

In older patients there may be some overlap with Alzheimer disease, as well as other causes of dementia such as vascular disease and Lewy body dementia.32 Indeed, several studies have shown a marked increase in minor cognitive impairment in HIV-seropositive individuals.32 In cases of viral suppression, there are no clear-cut additional ther-
apueutic measures that can be undertaken.

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The Research-Practice Gap

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to finding novel approaches to delivering treatment that can reach the vast number of individuals in need of care who currently receive no services at all.

Dr Fitzsimmons-Craft is Assistant Professor of Psychiatry, and Dr Wilfley is the Scott Rudolph Professor of Psychiatry, Medicine, Pediatrics, and Psychological and Brain Sciences, Washington University School of Medicine, St. Louis, MO. The authors report no conflicts of interest concerning the subject matter of this article.

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The Department of Psychiatry at the Zucker Hillside Hospital/Long Island Jewish Medical Center and Northwell Health is seeking a full-time board eligible/board certified psychiatrist to join our outpatient Perinatal Psychiatry Center. Though not a prerequisite, completion of advanced training in perinatal (reproductive) psychiatry and/or women’s mental health is preferred.

The Perinatal Psychiatry Center is a dynamic specialty Center within our comprehensive Adult Outpatient Psychiatry Department. This growing specialty Center articulates closely with our 22-bed inpatient psychiatry Women’s Unit with perinatal cluster in Zucker Hillside’s modern Behavioral Health Pavilion; with the Department of OB-GYN which delivers nearly 40,000 babies annually; with Northwell’s Katz Institute for Women’s Health; and with an elaborate Center articulates closely with our 22-bed inpatient psychiatry Women’s Unit with perinatal cluster in Zucker Hillside’s modern Behavioral Health Pavilion; and for participation in cutting-edge funded research protocols.

The successful candidate will join our multi-disciplinary behavioral health team of experts. Participants include psychiatrists, nurse practitioners, psychologists, social workers and licensed mental health counselors who collectively provide state-of-the-art diagnostics and therapeutics, including sensitive and informed psychopharmacological management for this patient population, and applicable evidence-based therapies.

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

**J-1 applicants welcome.**

For additional information, please contact:

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For more information, contact Steven Dingle, M.S., MD, Chief Medical Officer at steven.dingle@azdhs.gov or 602-220-6007.

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The School of Medicine will be the anchor in the development of a comprehensive health sciences campus that will also include research facilities and biotechnology endeavors – all in service of educating tomorrow's doctors, discovering novel therapies, and facilitating compassionate and effective healthcare that will meet the ever-changing needs of tomorrow's patients.

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OCEAN MEDICAL CENTER is a Hackensack Meridian Health ambulatory care hospital located in Lakewood, New Jersey. The hospital is a top performing, full-service 254-bed acute care hospital serving the healthcare needs of the community. Ocean Medical Center has been ranked as one of the safest hospitals in the state of New Jersey by Forbes Magazine.

Requirements: Candidates must have an MD or DO degree; Completion of an ACGME Accredited Psychiatry residency program. Experience as a member of a teaching faculty or as an educational administrative leader; and have a strong commitment to the development of healthcare and research thought leaders – all in service of educating tomorrow's doctors, discovering novel therapies, and facilitating compassionate and effective healthcare that will meet the ever-changing needs of tomorrow's patients.

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Ocean Medical Center's psychiatry program will be a community-based program,” said Ramon Solinhah, M.D., program director for psychiatry as well as founding Chair of Psychiatry & Behavioral Health at the Hackensack Meridian School of Medicine at Seton Hall University. "Our new psychiatry residency program will improve clinical care and ultimately encourage future health care leaders to build practices in the Jersey Shore area."

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- **Pediatric Psychiatry Collaborative**
- **Consultation Liaison Psychiatrists:**
  - o Hackensack University Medical Center (Hackensack, NJ)
  - o Raritan Bay Medical Center (Perth Amboy, NJ)
- **Staff Psychiatrist for Adult Inpatient Unit:**
  - o Riverview Medical Center (Red Bank, NJ)
  - o Hackensack University Medical Center (Hackensack, NJ)
- **Outpatient Child, Adolescent Psychiatrist:**
  - Hackensack University Medical Center (Hackensack, NJ)
- **Geriatric Psychiatry:**
  - Hackensack University Medical Center (Hackensack, NJ)

Renee.Theobald@Hackensackmeridian.org or call: 732 751-3597
HackensackMeridianHealth.org
We offer evidence of the largest comprehensive, multi-tiered program.

NORTH CAROLINA

State Hospitals/OMH NYC and Upstate

We Want You to Join Our Behavioral Health Team!

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

Behavioral Health Care is accredited by The Joint Commission and licensed by the State of North Carolina.

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

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

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

**Child Outpatient Opportunity**
- BE/BC Child & Adolescent providers. The current structure is for 90% outpatient Monday through Friday work schedule.

We offer best in class compensation plus generous benefits including Paid Malpractice, CME Time and Allowance, Accrued Paid Time Off, 403(b) match and 457(b), Health, Dental, and other desirable benefits.

Please contact Suzy Cobb, Physician Recruiter for more details at (910) 615-1889 or scobb2@capefearvalley.com.

OKLAHOMA

**Medical Director**

St. Mary’s Regional Medical Center, located in Enid, OK, is now hiring a Psychiatrist to provide inpatient and outpatient services. Enjoy providing much-needed services in an attractive Midwestern location work while benefitting from the support of a progressive administrative team that values a strong work/life balance.

**Opportunity Highlights**
- Hospital-employed position
- Position includes treatment of adult patients in a 15-bed inpatient wing as well as a busy outpatient practice
- Program is fully staffed and includes a receptionist, LPN and clinic manager.
- There is also an NP to assist the physician
- Position includes a Medical Directorship, with clinical oversight of the program
- Compensation package includes a competitive base salary, full employed benefits, sign-on bonus, relocation, and a director’s stipend.

St. Mary’s Regional Medical Center is a 229-bed facility and is one of the two hospitals in Enid. It serves a ten-county service areas with a population of approximately 200,000. Most specialties are represented on the medical staff.

Just 90 miles from Oklahoma City, Enid offers many of the advantages of larger cities without the associated high cost of living. One of Good Morning America’s “Five Hot Real Estate Markets”, Enid offers the best of Midwestern living - fine dining, shopping, historical sites, and recreational activities in abundance. If you’re looking for exceptional quality of life, consider Enid. You’ll see why we’re known as the “Bright Star of the Great Plains”!

For more information, contact: Mark Blakeney, Phone: 972.420.7473, or email: mark.blakeney@horizonhealth.com