

CHIEF EDITOR DR. SYED MUBIN AKHTAR

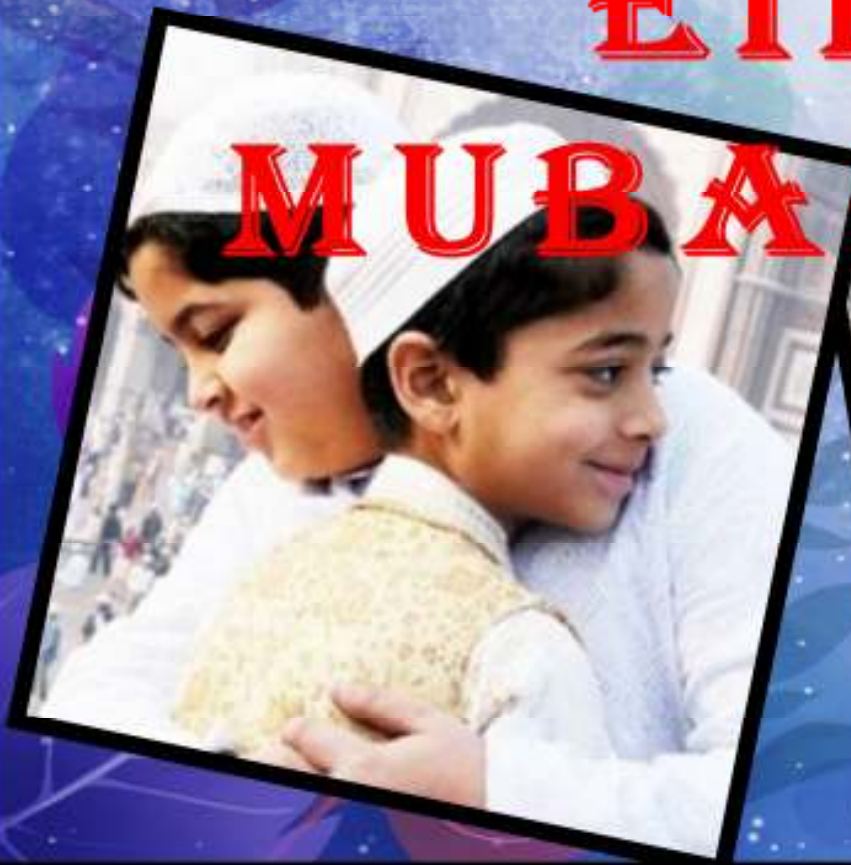
KARACHI
PSYCHIATRIC
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BULLETIN

(Psychiatric Research Articles)

JULY-2015

EID

MUBARAK



Award Ceremony

at Happy Dale School

Adopted by Dr. Syed Mubin Akhtar

Date: 29-05-2015



Dr. Syed Mubin Akhtar presenting gifts to Ms. Saghir Fatima (Principal), Ms. Rizwana Raza (Teacher) and Mr. Ghayoor Ali (Peon) on their best Performance.



Participants at Award Ceremony.



Participants at Award Ceremony.

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Clinical Issues and Strategies Associated With Smoking Cessation

Barbara Geller, MD reviewing Qiu A et al. *Transl Psychiatry* 2015 Feb 17.

Evidence for the need to screen for prenatal depression and anxiety becomes compelling.

Children of mothers who were depressed during pregnancy are at increased risk for depression (*J Affect Disord* 2009; 113:236), and depressed people across the age span have altered amygdala activity. Thus, several lines of evidence supported this investigation of amygdala function in infants.

Researchers assessed 24 pregnant women for depression at 26 months' gestation and at 3 and 12 months postnatally; their infants underwent structural and resting-state functional magnetic resonance imaging at 6 months. In analyses controlling for mothers' postnatal depressive symptoms, prenatal depressive-symptom scores correlated significantly with heightened left amygdala connections to multiple regions, including the anterior cingulate, insula, temporal cortex, and orbitofrontal cortex — i.e., regions affected in adult depression.

Unemployment Linked to Increased Suicide Risk Worldwide

Peter Roy-Byrne, MD reviewing Nordt C et al. *Lancet Psychiatry* 2015 Mar.

Consistent 20% to 30% increases in suicide with rises in unemployment rates are seen across multiple countries, age groups, and both genders.

Small, mostly single-country studies have shown the deleterious effects of unemployment on suicide risk. These researchers analyzed WHO mortality data and an International Monetary Fund economic outlook database for 2000–2011 to examine the effects of four economic indicators (unemployment, gross domestic product, growth rate, and inflation) on suicide rates across 63 countries, four age groups, and both sexes.

The investigators tried both linear and nonlinear models with and without various time lags. A nonlinear, 6-month time-lagged model gave the best fit, with suicide rates increasing 6 months before increases in unemployment rates. The effects were greatest when baseline unemployment rates were low. Suicide rates associated with heightened unemployment rates increased by 20% to 30%, regardless of country, age group, and sex. Links of suicide risk to other economic indicators were much less consistent.

Adding Chronotherapy or Exercise to Antidepressants for Major Depression

Joel Yager, MD reviewing Martiny K et al. Acta Psychiatr Scand 2015 Feb 17.

Remission rates were higher with adjunctive chronotherapy at 29 weeks than with an adjunctive exercise program.

Because major depression fails to remit with pharmacotherapy in many patients, several adjunctive nonpharmacological strategies have been investigated. Now, in a 29-week randomized trial involving 75 patients with persistent major depression (mean age, 48; mean age at onset of initial episode, 33; treatment resistance, 62%), researchers have examined the effects of medication plus either “chronotherapeutics” or exercise. The current episode had lasted >2 years in 24%; 16% of participants had bipolar I or II depression and were receiving mood stabilizers.

All participants received duloxetine at 60 mg/day for the first 9 weeks, with dosage increased to ≤ 120 mg/day (or the antidepressant changed) during the next 20 weeks, if necessary. The chronotherapy group completed three nights of forced wakefulness during week 2 and received 30 minutes/day of morning bright-light therapy during weeks 2 through 29. The exercise group received individually tailored exercise programs (duration, ≥ 30 minutes/day) with instructions to log their efforts, monthly supervisory visits with a physiotherapist, and extra physiotherapist sessions as needed.

By week 9, 30 chronotherapy patients and 34 exercise patients remained. At 29 weeks, response scores were similar between groups, but remission rates were higher for the chronotherapy group (62% vs. 38%). Sleep quality and duration improved more in those receiving chronotherapy. Treatment adherence was higher for chronotherapy than for exercise. The drop-out rate — 28% overall — was higher for chronotherapy than for exercise.

If It Were Physical Pain, It Would Be Called Torture: A Story of Two Young Men

When did human rights become negotiable in the US? When did human rights become a line item in a budget in the US? When did it become so difficult to simply do the right thing? Two recent newspaper articles portray how the seriously mentally ill have been systematically stripped of their human rights. By “human rights,” I mean the right to life and liberty.

The senator and his son

On November 1, 2014, The Washington Post ran an update on Virginia State Senator and former gubernatorial candidate, Creigh Deeds. One year earlier, his 24-year-old son almost killed him—before killing himself. In “A father’s scars: for Va’s Creigh Deeds, tragedy brings unending questions,” Stephanie McCrummen tells the story of what life is like now for the senator.

He gets out of bed, where a piece of the shotgun he had taken apart in those last days of his son’s life is still hidden under the mattress. He goes outside to feed the animals, first the chickens in the yard and then the horses in the red-sided barn. He leads the blind thoroughbred outside with a bucket of feed, the same bucket he was holding when he saw Gus walking toward him—“Morning, Bud,” he said; “Morning,” Gus said, and began stabbing him—and then he goes back inside.

The dismantling and closure of the federal and state mental hospitals beginning in 1955 has resulted in an extreme shortage of programs and facilities for troubled persons such as Austin “Gus” Creeds to be evaluated; treated as long as necessary, ideally to a reasonable assurance of long-term stability; or kept indefinitely if necessary. That patients in some state mental hospitals were poorly treated, mistreated, or maltreated in the past does not mandate that a new public mental hospital system would do so.

Opponents of reinvigorating the public mental hospital system argue for community programs. However, community programs are always vulnerable to state and local budget cuts; have not been demonstrated to be consistently effective at early identification and management of young persons with emerging psychoses, especially if no crimes have been committed; and cannot ensure the safety of persons such as Gus Creeds and their potential victims—the victims often being people they love. Community programs are important but serve a different purpose in the continuum of care for the severely mentally ill.

The college student and the county jail

The second article addresses where many of the seriously mentally ill are now found—if they have committed a crime: in our county jails, or for more serious crimes, in our state prisons. The Capital Times, a Madison, Wisconsin, weekly, published the following description of how life can be for the seriously mentally ill in a county jail—that life often being in solitary confinement.

In, “Boxed in: fighting for changes,” Sheriff Dave Mahoney calls his own jail “inhumane.” Steven Elbow describes the 4-day experience in solitary of Ian Olson, a 21-year-old college student at Macalester College. Ian was arrested for disorderly conduct after being disruptive and uncontrollable at a family gathering. This manic episode occurred because he had not taken his medication for bipolar disorder. It was the first time this had happened in 2 years of treatment. Judging from the date of his arrest, I am guessing that he discontinued his medications while studying for finals, or in conjunction with the end of his spring semester. This description of life in solitary confinement while psychotic is typical:

But he admits that on May 10, 2013, he was disruptive, insolent and uncontrollable, so much so that when he was taken to the jail, deputies abandoned the booking process and put him into Segregation Cell 1, a stark 6-by-9 foot room with a concrete bed, a thin green mattress, a steel toilet and sink, and a metal door with a small slot for food. The overhead light remained on 24 hours a day. On his first day, he flooded his cell by clogging the toilet, was placed in a “suicide smock,” and later strapped by the torso, ankles and wrists to a “violent prisoner restraint chair.” He didn’t eat, his water supply was cut off and he slept only sporadically.

Two different outcomes— both disturbing

The main difference between Ian Olson (college student) and Gus Deeds (senator’s son) is that Mr Olson had committed a crime, while Mr Deeds had not. Mr Olson lived, but endured 4 days of “inhumane treatment,” a euphemism for “torture.” This was caused by roadblocks for immediately admitting such patients to the barely functioning nearby state mental hospital. Such roadblocks are economically driven.

Mr Deeds died because of the same roadblocks. Time had run out on a court order remanding him to treatment at a state psychiatric hospital. There were no beds available at the time the order was obtained, and the legal limit in 2013 for holding someone while awaiting a bed, presumably someone dangerous to themselves or others, in North Carolina, was 6 hours. There are civil liberties reasons for limiting the length of psychiatric holds. However, dangerousness should trump civil liberties—especially when the currency is measured in hours—and psychosis with dangerousness is neither life nor liberty and is measured in lifetimes. If Mr Deeds had committed

a crime, perhaps he could have gone to solitary confinement at the county jail—experienced inhumane treatment there—and lived.

Inhumane treatment of the mentally ill—is this really who we are?

Sheriff Dave Mahoney in Wisconsin belongs in the same discussion as Dorothea Dix, a serious reformer who campaigned for the treatment of the seriously mentally ill in hospitals rather than have them languish in jails and prisons—often in solitary confinement—sometimes for years, occasionally for decades. The article referenced in The Capital Times includes a 2-minute video of Sheriff Mahoney, standing in one of the solitary confinement cells at the Dane County Jail, as he explains why we need to change the current system.

For every young adult from a socially and economically advantaged family, presumably capable of finding appropriate services, like the Deeds and Olson families appear to be, how many dozens, or hundreds, or perhaps thousands of such patients from disadvantaged families are being subjected to similar treatment and worse? Or living under a bridge suppressing their psychological pain with drugs and alcohol?

Real leaders do not compromise with right and wrong. Such leaders do not delay when “inhumane treatment” is occurring. Leaders educate constituents and advocate for justice. Leaders do the right thing oblivious to the electoral calculus. Leaders do not consider “inhumane treatment” to be a line item in a budget. A reinvigorated public mental hospital system would save the lives of people like Gus Creeds and the daily pain his parents still experience, as well as obviate the need to use solitary confinement for people like Ian Olson. Everyone has the right to life and liberty.

Intermittent Explosive Disorder

Psychiatric Times

March 25, 2015 | Special Reports, Neuropsychiatry, Trauma And Violence

By Emil F. Coccaro, MD

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Intermittent Explosive Disorder

Psychobiological Aspects of Antisocial Personality Disorder, Psychopathy, and Violence

A Call to Arms to Understand and Treat Aggressive Behavior

A disorder of impulsive aggression has been included in DSM since the first edition. In DSM-III, this disorder was codified as Intermittent Explosive Disorder (IED) and was thought to be rare. However, DSM criteria for IED were poorly operationalized and empiric research in IED was limited until the past decade, when research criteria were first developed. Subsequently, interest in disorders of impulsive aggression led to a series of epidemiological studies that documented IED to be as common as several other psychiatric disorders.

Other recent research indicates that criteria for IED best identifies a group of individuals with robust differences in clinical characteristics, neurobiological findings, and documented responsiveness to treatment. In addition, other data strongly suggest important delimitation from other disorders previously thought to obscure the diagnostic uniqueness of IED. These data, across many studies by a variety of investigators, led to newly revised criteria for IED in DSM-5.

What is impulsive aggression?

Human aggression constitutes a multidetermined act that results in physical (or verbal) injury to self, others, or things. It appears in several forms and may be defensive, premeditated (predatory),

or impulsive (nonpremeditated). When recurrent in frequency, the latter two forms are psychopathological. A converging pattern of data consistently points to critical differences between impulsive and premeditated aggression such that while the two may appear in the same individual at different times, the underpinnings of the two are quite different.

Because this article is confined to IED as defined in DSM-5, the focus is on impulsive aggression. The most critical aspect of this phenomenon is that acts of impulsive aggression represent a quick and typically angry response nearly always triggered by a social threat or frustration that is out of proportion to the situation. These aggressive acts may include verbal arguments, temper tantrums (with or without property damage or harm to others), property assault, or assault on people or animals. In fact, the severity of the aggressive outburst is less relevant than the fact that the aggressive behavior is “explosive.” Other important DSM-5 criteria specify that most of the aggressive outbursts are impulsive, cause distress to the individual or impairment in the psychosocial function of the individual, and are not due to another disorder (ie, do not occur exclusively during another disorder).

Epidemiology of IED

The National Comorbidity Survey Replication (NCS-R) reported a lifetime prevalence of IED in the US of 7.3% by “broad [DSM-IV] criteria” and 5.4% by “narrow criteria,” and past year prevalence of 3.9% and 2.7%, respectively. Inspection of the data reveals meaningful differences between the two IED types, with “narrow” IED being far more severe than “broad” IED.5 “Broad” IED stipulates only 3 aggressive outbursts during a lifetime; “narrow” IED requires at least 3 aggressive outbursts in a year.

DSM-5 criteria include both non-injurious and non-destructive aggressive outbursts, provided that they are quite frequent (ie, average of 2 outbursts per week for at least 3 months). The number of DSM-5 IEDs in the US is uncertain; however, a review of the raw data from the NCS-R study suggests that the lifetime prevalence of DSM-5 IED is likely to be between 2% and 3%.

Psychiatric comorbidity

Because impulsive aggressive behavior appears in patients with many diagnoses, most clinicians have been reluctant to make a diagnosis of IED in the absence of other psychiatric diagnoses. In fact, impulsive aggressive behavior is manifest in all humans early in life and before the onset of other psychiatric disorders. In the vast majority of people, impulsive aggressive behaviors diminish over time, frequently well before adolescence. In the adolescent supplement to the NCS-R, lifetime prevalence of DSM-IV IED by “narrow” criteria was 5.3%, similar to what was found in adults. Clinical studies suggest significant comorbidity of IED with mood disorders, anxiety disorders, and substance use disorders. In each case, with the exception of phobic anxiety disorders, the age of onset of IED is reported to be earlier than that of the comorbid disorder. This suggests independence of the disorders or that IED might be a risk factor for the comorbid disorder. A similar finding was found in a family history study of IED. Some argue that the diagnosis of IED should not be made in the presence of borderline personality disorder (BPD) or antisocial personality disorder (ASPD). However, when examined empirically, levels of lifetime aggressive behavior among “BPD/ASPD only” individuals are markedly lower than those among persons who also meet criteria for IED, indicating that both diagnoses should be made when criteria for both are met.

Medical comorbidity

There has been evidence for the association between impulsive aggression, and/or irritability, and cardiovascular morbidity for many years. A reanalysis of a large community data set has confirmed this relationship for DSM-IV IED. Specifically, the study noted that in individuals with IED, there

is an increased risk of coronary heart disease; hypertension; stroke; diabetes; arthritis; ulcer; headaches; and back/neck pain and other chronic pain. Another study reports a significant correlation between IED and diabetes.

A factor tying many of these conditions (eg, coronary heart disease, stroke, arthritis, ulcer) together may be abnormalities of immune function. A study found that levels of plasma inflammatory markers (C-reactive protein [CRP] and interleukin-6 [IL-6]) were higher in individuals with IED than in psychiatric and healthy controls. Moreover, a history of aggressive behavior has been shown to directly correlate with levels of CRP and IL-6. It is not known if these elevations are causal to aggression as suggested by animal studies or merely associated with aggressive behavior. In either case, additional studies are needed to determine whether there is a rationale to treat the low-grade inflammation that may be present in individuals with IED.

Developmental and familial correlates

IED appears in childhood and peaks in adolescence: studies of adults report the mean age of onset as the mid-teens; studies of adolescents report the mean age of onset at about 12 years. The average duration of IED ranges from more than 10 years to nearly the whole lifetime, which suggests a persistent and chronic course without treatment. A recent family history study reported that first-degree relatives of individuals with IED (probands) have about a 34% chance of also having IED compared with about 10% in controls. The increased familial risk of IED was not affected by comorbidity in the probands or in the individual relatives. This is consistent with observations from twin studies that report moderate degrees of genetic influence underlying measures of both aggression and impulsivity.

Psychosocial antecedents

A history of trauma in childhood has long been thought to be associated with the development of aggression later on in childhood and in adolescence. While few studies have been published in the area of IED, one community survey reported a significant association between DSM-IV IED in a South African sample. The findings indicate that trauma was more common among those with “narrow IED” who had a history of trauma associated with a crime, trauma to a close friend or family member, and multiple trauma (ie, 6 or more episodes).

Nickerson and colleagues reported that interpersonal traumas and traumas experienced early in life are particularly predictive of IED. A recent study showed higher scores on the Childhood Trauma Questionnaire (CTQ) and lower scores related to parental care in DSM-5 IED subjects than in both psychiatric and healthy controls. Notably, CTQ scores were correlated with hostile attribution bias scores that were significantly greater in individuals with DSM-5 IED. This is consistent with data that strongly suggest that trauma/maltreatment in childhood is associated with aggression in later childhood or adolescence and that this relationship is mediated by hostile attribution bias. While we may not be able to prevent trauma/maltreatment in childhood, it may be possible to intervene at the level of attribution bias and to reduce the propensity to be impulsively aggressive at a later time in life.

Sociodemographic correlates

Clinical studies of IED suggest a male to female ratio of about 2 to 1. This is only partially supported by data from community samples in which only a small number of studies report an excess of males to females (odds ratio = 1.4 to 2.3). Other sociodemographic factors (eg, age, race, education, marital status, occupational status, family income) indicate variable and only modest correlates with IED.

Psychological correlates

Not surprisingly, individuals with IED demonstrate abnormalities in a number of psychological areas. Compared with controls, individuals with IED have:

- Elevations of relational aggression aimed at damaging interpersonal relationships
- Elevations of hostile attribution bias, and negative emotional responding, to socially ambiguous stimuli
- Elevations of affective lability and affective intensity
- Immature defense mechanisms, including acting out, dissociation, projection, and rationalization

Most recently, individuals with IED have been reported to have reduced emotional intelligence. All of these abnormalities provide a rationale for psychological intervention, particularly those that focus on emotional and social information processing.

Neurobiological correlates

Neurobiological studies clearly show a bio-behavioral relationship between aggression and select brain chemicals, such as serotonin. Persons with IED are reported to have altered serotonin function compared with persons without IED, as evidenced by a reduction in the number of platelet serotonin transporters or in the magnitude of the prolactin response to the serotonin agent fenfluramine. Positron emission tomography studies report lower fluorodeoxyglucose utilization after fenfluramine in the frontal areas of the brain and lower fluorodeoxyglucose utilization after meta-chlorophenylpiperazine challenge in the anterior cingulate in IED/BPD subjects than in healthy controls.

Two ligand-binding studies have also reported alterations in the binding of ligands for the serotonin transporter and the serotonin 2a receptor. Serotonin transporter availability in the anterior cingulate was less in IED subjects than in controls; availability of serotonin 2a receptors in the orbitofrontal cortex was greater in IED subjects with current physical aggression than in those without current physical aggression and in healthy control subjects.

A functional MRI study showed that IED subjects had increased activation of the amygdala and reduced activation of the orbitofrontal cortex to angry faces compared with controls. Recent volumetric studies have also noted reduced gray matter volume in the orbitofrontal cortex, the medial prefrontal cortex, the anterior cingulate cortex, the insula, and the amygdala in IED subjects compared with controls.

Treatment

Double-blind, placebo-controlled, clinical trials in patients with impulsive aggression and/or IED have been conducted over the past decade. A reduction was seen in impulsive aggressive behavior after fluoxetine treatment in personality-disordered patients with IED. This was replicated in 2 other studies of fluoxetine. In another study, patients with cluster B personality disorder who had IED and were treated with divalproex were found to have a reduction in impulsive aggression. A significant reduction in impulsive aggression was seen with oxcarbazepine. Levetiracetam had no effect on aggression.

In a study of cognitive-behavioral therapy (CBT) versus wait-list control, impulsive aggression, anger, and hostile automatic thoughts were significantly reduced with CBT that included relaxation training, cognitive restructuring, and coping skills training. Fluoxetine and CBT had similar therapeutic responses (greater than 50% reduction in state aggression). Given that both modalities are likely working through different mechanisms, the combination of the two modalities may be more effective than either one alone. Further studies are needed to explore this hypothesis in a head-to-head comparison of these interventions.

4 New Concepts in Alzheimer Disease

Neurology Times

Alisa G. Woods, PhD

News | May 04, 2015 | Alzheimer disease

By Alisa G. Woods, PhD

Proteins linked in a pathway, drugs that may prevent memory loss, the positive role of sleep, a new memory app—check out these latest new concepts in AD diagnosis and treatment.

A new concept of Alzheimer disease (AD) that links proteins, drugs that block brain arginine prevent memory loss, the positive role of sleep in AD, a new memory app—these are the latest new concepts in AD diagnosis and treatment.

Turn the pages to find out more:

Protein Pathway Could Reconceptualize Alzheimer

- A concept of AD that links proteins together in a pathway has been proposed by researchers from the University of Cambridge.
- The researchers studied stem cells taken from the skin of persons with AD and differentiated them into neurons.
- Using medications that increase or decrease beta-amyloid processing, they found that processing from amyloid precursor protein (APP) may be directly linked to tau levels.
- The research underscores the possible use of stem cells in research and points toward possible normal as well as pathological functioning of beta-amyloid and tau in the nervous system.
- APP metabolism affects tau levels and may be targeted in future therapeutic interventions for AD.

Exploring the Role of Arginine in AD

- Previous drugs targeting beta-amyloid, the main implicated culprit in AD, have demonstrated limited success.
- Previous research on AD mouse models demonstrated low brain arginine.
- Duke researchers have found that mice with experimental AD (CVN-AD mice) have brains that consume excessive arginine via the enzyme arginase.
- Drugs that blocked brain arginine consumption via a specific immune system pathway prevented memory loss and brain cell death in the AD mice.
- Future studies of the strategy to target arginine consumption will proceed, perhaps ultimately also in humans.

Sleep Restores Memory in a Fly Model of AD

- Numerous studies have linked sleep to memory.
- A *Drosophila* (fruit fly) mutant that lacks a sleep promoting agent and also has memory problems has been studied by researchers at Washington University School of Medicine in St Louis.
- The researchers used 3 techniques to restore sleep in the flies:
 1. Brain cell stimulation.
 2. Increasing sleep promoting proteins.
 3. Giving the flies a medication that increased sleep.
- In all cases, the increase in sleep of about 3 or 4 hours daily also improved memory in the flies.
- The study has implications for the positive role of sleep in AD and reinforces that targeting sleep-related proteins may be a strategy for future AD treatments.

An App to Remember

- Smartphones and tablets can be used to help persons with AD remember.
- Samsung has released a "Backup" memory app to help persons with AD remember family members.
- The app detects nearby family members and identifies their name and relationship to the person with AD.
- Future versions of the app will include the names of nearby locations, using GPS.

Take-aways:

- A newly proposed concept of AD links proteins together in a pathway.
- Drugs that blocked brain arginine consumption via a specific immune system pathway prevented memory loss and brain cell death in AD mice.
- A study of fruit flies has implications for the positive role of sleep in AD and targeting sleep-related proteins for AD treatments in humans.
- A new memory app helps persons with AD remember family members.

The Narcissistic Cycle of Abuse

By Christine Hammond

~ 2 min read

The cycle of abuse Lenore Walker (1979) coined of tension building, acting-out, reconciliation/honeymoon, and calm is useful in most abusive relationships. However, when a narcissist is the abuser, the cycle looks different.

Narcissism changes the back end of the cycle because the narcissist is constantly self-centered and unwilling to admit fault. Their need to be superior, right, or in charge limits the possibility of any real reconciliation. Instead, it is frequently the abused who desperately tries for appeasement while the narcissist plays the victim. This switchback tactic emboldens the narcissist behavior even more, further convincing them of their faultlessness. Any threat to their authority repeats the cycle again.

Here are the four narcissistic cycles of abuse:

- **Feels Threatened.** An upsetting event occurs and the narcissist feels threatened. It could be rejection of sex, disapproval at work, embarrassment in a social setting, jealousy of other's success, or feelings of abandonment, neglect, or disrespect. The abused, aware of the potential threat, becomes nervous. They know something is about to happen and begin to walk on eggshells around the narcissist. Most narcissists repeatedly get upset over the same underlying issues whether the issue is real or imagined. They also have a tendency to obsess over the threat over and over.
- **Abuses Others.** The narcissist engages in some sort of abusive behavior. The abuse can be physical, mental, verbal, sexual, financial, spiritual or emotional. The abuse is customized to intimidate the abused in an area of weakness especially if that area is one of strength for the narcissist. The abuse can last for a few short minutes or as long as several hours. Sometimes a combination of two types of abuse is used. For instance, a narcissist may begin with verbal belittling to wear out the abused. Followed by projection of their lying about an event onto the abused. Finally tired of the assault, the abused defensively fights back.

- Becomes the Victim. This is when the switchback occurs. The narcissist uses the abused behavior as further evidence that they are the ones being abused. The narcissist believes their own twisted victimization by bringing up past defensive behaviors that the abused has done as if the abused initiated the abuse. Because the abused has feelings of remorse and guilt, they accept this warped perception and try to rescue the narcissist. This might include giving into what the narcissist wants, accepting unnecessary responsibility, placating the narcissist to keep the peace, and agreeing to the narcissistic lies.
- Feels Empowered. Once the abused have given in or up, the narcissist feels empowered. This is all the justification the narcissist needs to demonstrate their rightness or superiority. The abused has unknowingly fed the narcissistic ego and only to make it stronger and bolder than before. But every narcissist has an Achilles heel and the power they feel now will only last till the next threat to their ego appears.

Once the narcissistic cycle of abuse is understood, the abused can escape the cycle at any point. Begin by coming up with strategies for future confrontations, know the limitations of the abused, and have an escape plan in place. This cycle does not need to continue forward.

Prenatal Air Pollutants May Affect Brain Development

Christine Fox, MD, MAS reviewing Peterson BS et al. JAMA Psychiatry 2015 Mar 25.

Polycyclic aromatic hydrocarbon exposure in pregnancy correlates with morphologic white matter changes on brain neuroimaging during childhood.

Polycyclic aromatic hydrocarbons (PAHs) are air pollutants from sources such as diesel- and gasoline-powered vehicles, oil and coal combustion, and tobacco smoke. In this study, researchers asked whether exposure to PAHs during pregnancy could affect childhood brain morphology, measured by magnetic resonance imaging (MRI).

The researchers recruited nonsmoking African American or Dominican women from New York City prenatal clinics to complete an exposure questionnaire and wear a monitor for 48 hours during the third trimester of pregnancy to estimate PAH exposure. The researchers identified a subcohort of the women's children with a range of prenatal PAH exposure but low exposure to other toxic chemicals. From this group, 40 children underwent brain MRI and behavioral testing around 8 years of age.

The researchers found that increased prenatal PAH exposure correlated with reduction in left-hemisphere white-matter surface measurements and with slower information processing speed on the Wechsler Intelligence Scale for Children.

Quality improvement in neurology

Epilepsy Update Quality Measurement Set

Epilepsy is a common, debilitating, and costly disease. It is estimated that 2.2 million people in the United States are diagnosed with epilepsy, and 150,000 new cases of epilepsy are diagnosed in the United States annually. However, epilepsy prevalence might be underestimated due to numerous social issues that accompany a diagnosis of epilepsy. People with epilepsy have poorer overall health status, impaired intellectual and physical functioning, and a greater risk for accidents and injuries. It is estimated that the annual direct medical cost of epilepsy in the United States is \$9.6 billion, and this estimate does not include indirect costs from losses in quality of life or productivity.

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Brain death declaration

Practices and perceptions worldwide

1. Sarah Wahlster, MD,
2. Eelco F.M. Wijdicks, MD, PhD,
3. Pratik V. Patel, MD,
4. David M. Greer, MD, MA,
5. J. Claude Hemphill III, MD, MAS,
6. Marco Carone, PhD and
7. Farrah J. Mateen, MD, PhD

ABSTRACT

Objective: To assess the practices and perceptions of brain death determination worldwide and analyze the extent and nature of variations among countries.

Methods: An electronic survey was distributed globally to physicians with expertise in neurocritical care, neurology, or related disciplines who would encounter patients at risk of brain death.

Results: Most countries (n = 91, response rate 76%) reported a legal provision (n = 63, 70%) and an institutional protocol (n = 70, 77%) for brain death. Institutional protocols were less common in lower-income countries (2/9 of low [22%], 9/18 lower-middle [50%], 22/26 upper-middle [85%], and 37/38 high-income countries [97%], $p < 0.001$). Countries with an organized transplant network were more likely to have a brain death provision compared with countries without one (53/64 [83%] vs 6/25 [24%], $p < 0.001$). Among institutions with a formalized brain death protocol, marked variability occurred in requisite examination findings (n = 37, 53% of respondents deviated from the American Academy of Neurology criteria), apnea testing, necessity and type of ancillary testing (most commonly required test: EEG [n = 37, 53%]), time to declaration, number and qualifications of physicians present, and criteria in children (distinct pediatric criteria: n = 38, 56%).

Conclusions: Substantial differences in perceptions and practices of brain death exist worldwide. The identification of discrepancies, improvement of gaps in medical education, and formalization of protocols in lower-income countries provide first pragmatic steps to reconciling these variations. Whether a harmonized, uniform standard for brain death worldwide can be achieved remains questionable.

Opioid Use Disorder: Update on Diagnosis and Treatment

Psychiatric Times

Christina Brezing, MD

Adam Bisaga, MD

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By Christina Brezing, MD and Adam Bisaga, MD

While opioid dependence is among the most severe and lethal of addictions, it also has the most effective medication treatments. The authors provide 2 case vignettes and a step-by-step process for clinical decision making.

Over the past 10 years, the prevalence of heroin and prescription opioid misuse has significantly increased, in large part because of the increased prescribing of opioid analgesics in the US. As a result, there has been an unparalleled rise in the number of people affected with opioid use disorders and great concerns about the associated morbidity and mortality—including opioid-related overdoses and deaths in conjunction with the spread of infectious diseases, such as HIV infection and hepatitis C.

In this environment, it is imperative that physicians, particularly psychiatrists, are able to identify opioid use disorders; provide education and strategies for harm reduction; and offer effective, evidence-based treatments.

In this brief overview, we provide a step-by-step process for clinical decision making with 2 common-scenario case vignettes.

CASE VIGNETTE

Mr Gordon is a 45-year-old construction worker who had been injured a year earlier when picking up a heavy piece of equipment. His primary care physician (PCP) prescribed oxycodone for the pain. After 3 months, the original dose prescribed no longer controlled his pain, and Mr Gordon began gradually increasing the dose and subsequently running out of his medication earlier than anticipated. After multiple discussions about his increasing use of oxycodone and his failed attempts to cut down on his use, Mr Gordon's PCP stopped prescribing the medication.

After using the last dose of oxycodone, Mr Gordon woke up sweating profusely, with diarrhea, nausea, bone aches and pains, and anxiety. The next morning, he experienced very strong urges to use oxycodone, and he made 3 appointments with different physicians and managed to obtain prescriptions from each of them. In addition, he began buying "blue roxies" (colloquial term for oxycodone 30-mg tablets) from a neighbor, and learned to crush and use 5 to 8 tablets intranasally daily, noting a faster onset of effect.

In a short time, Mr Gordon found himself frequently calling in sick to work so he could continue using the pain-killers. He felt sick on the mornings when he did not have enough pills. He also became depressed and uninterested in socializing, and he had poor appetite and no sex drive. He stopped going to the gym, which had previously been his passion.

After missing work for the third time in a week, he was fired. Out of work and with only a few tablets of oxycodone left, Mr Gordon feels that his use of oxycodone is out of control and that he has become "a different person."

Mr Gordon's diagnosis

In DSM-5, opioid use disorders, like all substance use disorders, have been redefined as a spectrum of pathology and impairment. The criteria for an opioid use disorder are generally the same as in DSM-IV. The diagnostic criteria for DSM-IV abuse and dependence were combined in DSM-5 except for 2 changes: (1) the criterion for recurrent legal problems has been removed and (2) a new criterion for craving, or a strong desire or urge, to use opioids has been added (see Table 1 for all 11 criteria).

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

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

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

Treatment options

In the US, there are 3 FDA-approved medication treatments for opioid use disorders, all of which engage the μ -opioid receptor: methadone, a full agonist; buprenorphine, a partial agonist; and naltrexone, an antagonist. Table 2 compares the different properties of each medication. While methadone is an effective pharmacological option, because of federal regulations, it is only available at designated methadone administration sites (methadone maintenance treatment programs) and is not available for the treatment of opioid use disorders by prescription.

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

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

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

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

Physicians who are interested in using buprenorphine to treat patients with opioid use disorders can obtain a DATA 2000 (Drug Addiction Treatment Act of 2000) waiver by completing training and submitting their waiver of intent as outlined by the Substance Abuse and Mental Health Services Administration (SAMHSA). Training can be completed in person or online (pcssmat.org). The Drug Enforcement Administration will subsequently provide the physician with a separate license number (X-number) to be used when writing buprenorphine prescriptions. Naltrexone binds to the μ -opioid receptor with a high affinity but does not exert any activity; rather, it prevents binding of agonists or displaces agonists at the receptor. Naltrexone can be administered after detoxification to prevent relapse, when it provides a complete blockade of opioid effects. Naltrexone is available in an oral tablet formulation that requires daily administration or a once-monthly, long-acting intramuscular injection (Vivitrol) to bypass the difficulties with adherence to daily medication that many patients have at treatment outset. No additional training or licensure is required to prescribe naltrexone for opioid use disorders, but training materials are available (pcssmat.org).

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

Treatment course

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

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

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

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

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

CASE VIGNETTE

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

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

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

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

After her discharge and a total of 6 months abstaining from opioids, she relapsed with oxycodone and benzodiazepines—she notes that she felt "bored" at work and was seeking excitement. She overdosed during the first week, and a friend called an ambulance after she became nonresponsive. This overdose prompted Ms Derbin to seek treatment again—this time as an outpatient with buprenorphine induction and maintenance. She did well for 2 months while taking buprenorphine, using heroin only occasionally, but she continued to use cocaine and alprazolam. Eventually she began diverting the buprenorphine and attempting to inject it. After 1 month, she stopped injecting buprenorphine and resumed daily injections of heroin. She presents to you with concerns about her injection use. She wants to be detoxified because she does not want to be "dependent on any substance ever again."

History informs treatment considerations

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

Detoxified individuals are at greater risk for overdose than those who avoid treatment and continue to use opioids regularly. Individuals who use opioids in the context of sedative and alcohol use are at the highest risk for respiratory suppression and overdose. All opioid users, especially those who decline further treatment following detoxification, should be counseled about the high risk of overdose with relapse and provided with a naloxone rescue kit. Their friends and family need to be educated about how to obtain a rescue kit (SAMHSA Opioid Overdose Toolkit; projectlazarus.org) and about how to administer the naloxone in the event of an overdose. Patients who inject opioids should also be informed about clean needle exchanges.

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

Transitioning to antagonist treatment

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

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

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

Ms Derbin's treatment course

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

As she became more engaged in the relapse-prevention behavioral therapy over time, she lost cravings for the drugs and now only uses marijuana with decreased frequency (from daily use down to 4 times a week). She has been abstinent from opioids for 18 months with ongoing monthly injections of naltrexone. At present, Ms Derbin reports much greater stability than with previous

treatment attempts. When she started working, her PCP prescribed extended-release stimulants to treat symptoms of her ADHD. Ms Derbin reports improvement in work and life satisfaction. She broke up with the heroin-using boyfriend and began attending regular Narcotics Anonymous meetings, at which she has found a community of people she identifies with in recovery.

Conclusions

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

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

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

Psychotropic Medication Use During Pregnancy: Between a Rock and a Hard Place

Barbara Geller, MD reviewing Sutter-Dallay A-L et al. J Clin Psychiatry 2015 Mar 31.

In seriously ill women, prenatal use of certain drugs was associated with low birthweight or neonatal hospitalization.

Few studies on the adverse effects of prenatal psychotropics have included patients with serious psychiatric illness. The current investigators retrospectively evaluated prenatal psychotropic use and neonatal outcomes in 1071 women with major psychiatric disorders who were hospitalized postpartum in specialized units with their newborns in France between 2001 and 2010.

Data included maternal interviews and birth records, but not dosages and blood levels. Forty percent of women received psychotropics during pregnancy. Analyses compared the 40% of women who received psychotropics with nonrecipients and controlled for multiple variables, including those more frequent among psychotropic recipients (smoking, lower education, and multiparity).

Risk for low birth weight (<2500 g) increased with use of mood stabilizers. Risk for neonatal hospitalization increased with use of antipsychotics, antidepressants, or hypnotics/anxiolytics. Risk for preterm birth (gestational age, <36 weeks) was not affected by psychotropic use. Risks did not vary by diagnosis of schizophrenia, bipolar disorders, or substance use disorders.

Bipolar Disorder Is Bad for Your Health

Jonathan Silver, MD reviewing Kessing LV et al. Bipolar Disord 2015 Apr 4.

Life expectancy is shortened, no matter the patient's age at diagnosis.

As with schizophrenia, bipolar disorder has been associated with elevated mortality. However, much of that research has been based on patients with early onset disease (age, <15 years). These researchers used Danish nationwide registries to examine life expectancy in patients diagnosed throughout the lifespan. The data covered all 22,752 individuals with inpatient or outpatient diagnoses of bipolar disorder from 1970 through 2012 who were alive in 2000 (13,650 women). Regardless of age at diagnosis, life expectancy in patients was less than in the general Danish population. However, as age at diagnosis increased, the differences gradually diminished, as did the ratio of life expectancy in the bipolar group to that in the general population. For those diagnosed by age 15, the ratio of life expectancy was 79% in men (a difference of 13 years) and 84% in women (a difference of 10 years). For those diagnosed at age 75, the ratio was 71% in men (difference, 3 years) and 74% in women (difference, 3 years).

D-Cycloserine Works for Children with Specific Phobia, Too

Deborah Cowley, MD reviewing Byrne SP et al. *Depress Anxiety* 2015 Mar 10.

Used before exposure therapy, it enhances fear extinction in children with dog or spider phobias. The partial N-methyl-D-aspartate receptor agonist D-cycloserine (DCS) enhances consolidation of the learning of fear extinction and facilitates exposure treatment for anxiety in adults. These researchers examined effects of DCS in 35 children with dog or spider phobias (age range, 6–14 years; 21 girls).

The children did not have significant depression, psychosis, panic symptoms unrelated to their phobia, or pervasive developmental disorder. None were receiving antidepressants or other treatment for the phobia. They were randomized to a single dose of DCS (50 mg) or placebo 1 hour before exposure therapy (typical duration, 1 hour) to a feared stimulus. Approximately 1 week later, they were exposed to a different feared stimulus, in the same context and in a novel one.

DCS was well-tolerated. Both DCS and placebo groups displayed similar fear extinction after the first exposure session and 1 week later, when a new stimulus was presented in the same setting. When the new stimulus was presented in a novel context, the DCS group displayed less fear and avoidance than the placebo group.

Heavy Drinking and Mental Health Problems: Which Comes First?

Deborah Cowley, MD reviewing Bell S et al. *Alcohol Clin Exp Res* 2015 Mar 19.

Mental health was the underlying factor in this 10-year study of heavy drinkers.

The comorbidity of heavy alcohol consumption and mental health problems has been theorized to be due to alcohol use, to result from mental illness, or to represent a reciprocal relationship between the two. Investigators examined these interrelationships in 500 untreated heavy drinkers in the U.K. (men, 74%; white, 91%; mean age, 37.6; employed, 57%; mean heavy drinking days, 16/month).

During a 10-year period, participants were interviewed every 2 years about drinking and completed mental health questionnaires; 52% participated in the final assessment. After controlling for multiple confounding variables (demographics, employment, smoking, illicit drug use, and physical health) and considering dynamic changes over time, the researchers found that mental health symptom scores influenced changes in frequency of heavy drinking days, and not vice versa.

Which Elements of Dialectical Behavior Therapy Are the Most Beneficial?

Steven Dubovsky, MD reviewing Linehan MM et al. *JAMA Psychiatry* 2015 Mar 25.

Skills specific to DBT seem to be central to improvement in suicidality.

Dialectical behavior therapy (DBT) reduces suicidality and treatment dropout in patients with borderline personality disorder (BPD). The group that introduced DBT conducted a prospective, randomized study of different combinations of DBT components in 99 women with BPD (mean age, 30) matched for relevant clinical factors. Most participants had at least two suicide attempts or episodes of nonsuicidal self-injurious behavior (NSSI) within the past 2 years and at least one more-recent event.

The study included 1 year of treatment and another year of follow-up. Treatment arms were standard DBT (individual therapy, group skills training, between-session coaching, therapist consultation), DBT-I (individual therapy focused on skills that patients already have, a nonspecific activities group, no teaching of new DBT skills), and DBT-S (group training in DBT skills, case management, no individual therapy).

All three treatments significantly reduced suicidality. DBT and DBT-S were more effective than DBT-I (which lacked skills training) in reducing NSSI in year 1. DBT and DBT-S also resulted in more improvement in depression and anxiety during treatment, but DBT-I patients caught up during the follow-up year. Also during follow-up, emergency department visits and psychiatric hospitalizations were half as frequent after DBT than after DBT-I.

How Do Rapidly Acting Antidepressants Differ from Traditional Ones?

Peter Roy-Byrne, MD reviewing Stuart SA et al. *Neuropsychopharmacology* 2015 Mar 25.

This animal study suggests that ketamine improves depression by acting on cortical areas modulating subcortical emotional centers, whereas venlafaxine acts directly on the subcortical emotional centers themselves.

Recent efforts to develop rapidly acting antidepressants have highlighted the effects of ketamine, which both works quickly and seems to help severely treatment-resistant depressed patients. Because depressed patients have a bias to attend to negative information, researchers receiving some industry support explored the neural basis of ketamine and venlafaxine effects in an animal study using a novel “affective bias” paradigm.

The paradigm used separate exposures to medication and stress to induce a negative bias in rodents. Ketamine immediately reversed this acquired affective bias, but venlafaxine did not. When given before training, venlafaxine (but not ketamine) prevented the development of affective bias. The researchers examined mechanisms of action via brain lesions or drugs directly infused into specific brain areas. The effects of ketamine were localized to the prefrontal cortex, whereas the effects of venlafaxine were localized to the amygdala.

Helping Parents Achieve Behavior Modification in Children with ASD

Martin T. Stein, MD reviewing Bearss K et al. *JAMA* 2015 Apr 21.

A behavioral training intervention was more effective than an educational program, which also improved behaviors.

Parent training programs in behavior modification for children with autism spectrum disorder (ASD) have been demonstrated effective in several small studies. Are parent educational programs similarly effective?

To compare the effectiveness of parent training and parent education in modifying ASD-associated disruptive behaviors, investigators randomized 180 children aged 3 to 7 years with ASD to parent training or structured parent education for 24 weeks. Training consisted of 11 to 13 sessions, 2 telephone sessions, 2 home visits, and 6 child-parent coaching sessions. Training comprised standard behavior management training with a focus on analyzing antecedents and consequences of behavior followed by strategies to prevent disruptive behaviors. Education included 12 sessions and 1 home visit in which parents were given information about developmental changes in children with ASD, educational planning, advocacy, and treatment options. Behaviors were assessed before and after each intervention using two standardized, parent-completed questionnaires; in addition, a clinician blinded to intervention status rated improvements using the Clinical Global Impression scale.

At 24 weeks, both groups showed significant declines in disruptive and noncompliant behaviors, but improvements in questionnaire scores were significantly greater in the training group versus

the education group (48% vs. 32% on one scale and 55% vs. 34% on the other scale). Although these changes in behavior were statistically significant, the authors concluded that these differences were of minimal clinical importance. The clinician-generated scale showed significantly improved behaviors in both groups (69% for training and 40% for education).

Want to Stop Drinking? Don't Smoke

Steven Dubovsky, MD reviewing Leão RM et al. J Neurosci 2015 Apr 15.

In animals, the combination of alcohol and nicotine dysregulates behavior and networks of cognition, negative affect, and incentive salience.

To determine why alcoholism is more common in smokers, researchers conducted an animal study. Rats were trained to press a bar to obtain alcohol and were then given daily nicotine or saline in various experimental protocols. Some animals were made physically dependent on alcohol. Especially in alcohol-dependent animals, nicotine increased the rate at which alcohol intake increased, the amount of work that animals would do to obtain alcohol (i.e., the number of times they would press a bar to get one dose), and the amount of drinking despite adverse consequences (alcohol was adulterated with quinine, which rodents normally do not like).

In neuropathological studies, the combination of alcohol and nicotine recruited discrete neuronal ensembles comprising 4% to 13% of neurons in elements of the amygdala, dorsal corticostriatal module, and mesolimbic posterior ventral tegmental area. A nicotinic cholinergic antagonist blocked the neuropathological and behavioral changes.

Gender Cognition in Transgender Children

1. Kristina R. Olson
2. Aidan C. Key
3. Nicholas R. Eaton
 1. Department of Psychology, University of Washington
 2. Gender Diversity, Seattle, WA
 3. Department of Psychology, Stony Brook University
1. Kristina R. Olson, University of Washington, Department of Psychology, P. O. Box 351525, Guthrie Hall, Seattle, WA 98195 E-mail: krolson@uw.edu
1. Author Contributions All three authors designed the measures and wrote the manuscript. K. R. Olson led data collection and analysis.

Abstract

A visible and growing cohort of transgender children in North America live according to their expressed gender rather than their natal sex, yet scientific research has largely ignored this population. In the current study, we adopted methodological advances from social-cognition research to investigate whether 5- to 12-year-old prepubescent transgender children (N = 32), who were presenting themselves according to their gender identity in everyday life, showed patterns of gender cognition more consistent with their expressed gender or their natal sex, or instead appeared to be confused about their gender identity. Using implicit and explicit measures, we found that transgender children showed a clear pattern: They viewed themselves in terms of their expressed

gender and showed preferences for their expressed gender, with response patterns mirroring those of two cisgender (nontransgender) control groups. These results provide evidence that, early in development, transgender youth are statistically indistinguishable from cisgender children of the same gender identity.

Prenatal Cocaine Is Bad for the Baby's Brain

Steven Dubovsky, MD reviewing Salzwedel AP et al. J Neurosci 2015 Apr 8.

Some neonatal functional connectivity abnormalities were specific to cocaine and might explain enduring problems of attention and arousal found in older children with prenatal cocaine exposure. Children born to mothers who used cocaine during pregnancy exhibit abnormalities of attention and arousal that persist at least into adolescence. To understand why, investigators performed functional magnetic resonance imaging on infants with prenatal exposure to cocaine alone or with other substances (PCE; n=45), to substances other than cocaine (alcohol, marijuana, nicotine, antidepressants; NCOC; n=43), or to no drugs (n=64). Postnatal drug exposure through breastfeeding was minimal, except for nicotine, used by 17 women. Use of substances other than cocaine was similar in the PCE and NCOC women.

On average, PCE infants were born 7 days earlier and 14 oz lighter than infants without cocaine exposure. In analyses controlled for relevant clinical and demographic factors, the two drug groups showed similarly altered connectivity between amygdala-frontal, insula-frontal, and insula-sensorimotor networks. However, the PCE group, compared with the NCOC group, showed significantly different connectivity between the left amygdala and a frontal subcluster. Findings were independent of the amount of cocaine used.

Using Psychodrama to Teach CBT

Psychiatric Times

Sharon Packer, MD

April 29, 2015 | Cognitive Behavioral Therapy, Challenging Cases, Depression, Major Depressive Disorder, Psychotherapy

By Sharon Packer, MD

Is it possible to add creative twists to proven therapeutic techniques in order to encourage reluctant patients to try safe and effective treatments that we believe can benefit them? After reading the case, tell us what you think.

CHALLENGING CASE

Is it possible to add creative twists to proven therapeutic techniques in order to encourage reluctant patients to try safe and effective treatments that we believe can benefit them? After reading the case, tell us what you think in the comments section at the end of this article.

CASE VIGNETTE

"Danny" (identity changed) was a delightful person, and talented to boot, but self-effacing to a fault. The years he spent with embittered parents had taken their toll. Antidepressants increased his energy but did not erase Danny's negative self-talk. Psychodynamic therapy identified the origins of his self-doubt, but it did not dampen his deafening internal dialogue.

Danny had grown up in the Deep South, not rich, but not as poor as some of his neighbors. When a big box store opened across the river, his family's small fishing supply shop could not compete. It lost its customer base and closed in 2 seasons. The family store was not large, by Danny's accounts, but it fed the family and paid for Danny's after school classes. His father had inherited the store from more enterprising grandparents who were long gone. Now the store was gone, and Danny's father needed a job.

Father was too proud to accept a job at the big box store and he found no other opportunities. He lacked the spark that had propelled his own father into opening a business. He berated his wife for offering to work as a cashier at that same store. So Dad fished all day, returned home at night, and shouted at his sons, reminding Danny that he would never amount to anything. No wonder Danny left town when he had a chance. He took a job as a stagehand with a traveling theater company. He ended up in New York City.

Danny's sense of inadequacy continued, unabated. It was obvious that he incorporated his father's insults into his self-image, but understanding that father projected his own failures onto his son did not relieve Danny's distress. Danny's negative self talk seemed suited to a trial of cognitive behavioral therapy (CBT).

When Danny looked skeptical, I elaborated on the value of identifying distorted cognitions and arguing against them. "Ignoring the evidence" is first on a short list of common cognitive errors. (Other recurring cognitive errors include magnifying or minimizing, jumping to conclusions, catastrophizing, and so on.)

The very word, "evidence," reminded me of Law & Order, a long-running television program that recently celebrated its 25th year on the air. I heard myself saying to Danny, "You know, like on Law & Order."

I myself was not a diehard Law & Order fan (and am not even a TV watcher), but my sister developed an unnatural affection for the series, in spite of her PhD in epidemiology. Dinner at my sister's house meant listening to Law & Order playing in the background. As a result, Law & Order started playing in the background of my own mind (not as an hallucination, but as a free association!) as we spoke of "evidence." Since Danny worked for a theater company, this association became even stronger.

I asked Danny to pretend to be the prosecutor on Law & Order and to poke holes in the witness' statements. Danny pointed out that he already acted as the "witness" as he "testified" to "facts" about his predicted failures. Since this was not a real court, I convinced him to continue his questioning, without giving up until he—the witness—caves in and admits that his statement contradicts other "evidence."

In this case, the "allegation" concerned Danny's alleged inability to hold a job. He always expected to be fired. Yet the "evidence" proved that Danny could indeed hold a job (unlike his explosive father).

To make matters more fun, I suggested that he pretend to be the defense counsel who must support his witness's assertions, however absurd. That role offers an opportunity to defend reflexive—but maladaptive—responses, and often reveals little or no evidence to support automatic bad thoughts. We proceeded, "Law & Order-style," talking about his expectations. The next time he tried to "jump to conclusions," (which is a common cognitive distortion), Danny was told to jump in like a Law & Order attorney and complain, "Counsel is leading the witness." At this point, the judge intervenes.

With a little practice, Danny learned to be his own judge and to intervene in his mind's "courtroom proceedings." He matched his automatic responses to other distorted cognitions on the list from

my APPI-press book on High-Yield Cognitive-Behavioral Therapy, such as "jumping to conclusions," "over-generalizing," "catastrophizing" or "expecting their worst," "all-or-none thinking," or "personalizing." Danny did his homework, shared it with friends, and apparently had fun.



©jslavy-shutterstockHow would you proceed?

A. I would try to teach new CBT techniques, even though there are obvious obstacles

B. I would not try CBT before exhausting trials of all available psychopharmaceutical strategies, including adding lithium or second-generation antipsychotics approved as antidepressant adjuncts to his antidepressant regimen or then doing a washout of all medications so he can start monoamine oxidase inhibitors

C. I would refer him for more intensive and longer term therapy at a local psychoanalytic training institute that offers several psychoanalytic sessions per week for up to 2 years, especially since the psychodynamic

origins of his self-doubt seem so transparent

D. I accept the fact that some patients can improve only so much and feel fortunate that he is able to hold a full-time job

E. I would "reframe" the CBT techniques in terms that he can relate to, using contemporary media, rather than presenting CBT techniques as demanding educational exercises

[Please include full names names and academic titles in your comments. –Psychiatric Times Editors]

Discussion

There is a lesson to be learned from Danny's success at this modified approach to CBT. It should not come as a surprise that many patients do not complete CBT homework assignments. Schoolteachers (and perhaps parents) could have predicted this, but health care professionals must measure results. As an example, data show that only a small fraction of patients do CBT "assignments" for substance use. There is more discord about how much is enough—or good enough—homework.

Many studies confirm the efficacy of CBT, yet people are people, and even adult patients are not always as diligent as they could be. In contrast, it is common to encounter patients who exclaim, "I can't believe it—that's so me!" when handed the list of "Distorted Cognitions," downloaded from the CBT book referenced below. The next challenge is convincing patients to argue against their automatic thoughts at the time they occur, so that they can extinguish the distorted cognition and substitute a more accurate and adaptive idea, to the point that this becomes habit. Turning this assignment into a game, rather than a task, makes it easier to complete.

Teachers learned a long time ago that "edutainment" succeeds more than ordinary education. They have to engage their students, just as we must engage our patients. We no longer expect school students to memorize long Latin conjugations to "train their minds." Why should we expect more from our patients, who may be more anxious, depressed, or distracted than average students? By making their CBT assignments fun, we stand a better chance of helping them benefit from scientifically proven techniques. It is unlikely that incomplete CBT assignments are more helpful than unfilled prescriptions.

Admittedly, not everyone likes Law & Order, but enough do, making it worth analyzing. This brief case example suggests that this modified CBT technique deserves further study. However, I must

confess: this approach is just old-fashioned psychodrama blended with contemporary CBT—but next to no one knows about psychodrama anymore and almost everyone knows about Law & Order. My next assignment for myself is to find more ways to spruce up CBT to match other patients' interests.

In spite of prior treatment with psychotropic medications and psychodynamic psychotherapy, this patient's nagging self-doubt and self-denigration persisted long after the vegetative and affective symptoms of depression remitted. He is skeptical that another type of treatment can relieve his distress. Because he is so self-critical, he is especially uncertain that he can do CBT lessons "correctly" and warns that such failure may worsen his low self-esteem.

Disclosures:

Dr Packer is Assistant Clinical Professor of Psychiatry and Behavioral Sciences at the Albert Einstein College of Medicine in the Bronx, NY. She is the author of several books, including, *Cinema's Sinister Psychiatrists: From Caligari to Hannibal* (McFarland, 2012) and *Neuroscience in Science Fiction Films* (McFarland, 2015). She is in private practice in New York City. She reports that she receives royalties from *Neuroscience in Science Fiction Films; A History of Evil in Popular Culture: What Hannibal Lecter, Stephen King, and Vampires Reveal About America* (ABC-CLIO, 2014); *Cinema's Sinister Psychiatrists, Movies and the Modern Psyche* (Praeger, 2007); and other books that do not relate to the topic at hand.

Borderline Personality Disorder Could Be a Syndrome of Emotional Dysregulation

Steven Dubovsky, MD reviewing Schulze L et al. *Biol Psychiatry* 2015 Apr 7.

Altered brain activations in response to negative stimuli are linked to abnormal gray matter volumes in areas related to emotion processing.

The debate continues about whether borderline personality disorder (BPD) is a distinct disorder or an aggregation of features seen in other conditions (*NEJM JW Psychiatry* Jul 2011 and *Acta Psychiatr Scand* 2011; 123:349). A meta-analysis has now provided additional insights.

There were 19 functional magnetic resonance imaging studies of 281 patients with BPD (defined by DSM-III or later) and 293 controls, plus 10 studies of gray matter volume (GMV) in 263 BPD patients and 278 controls. In unmedicated BPD patients versus controls, activation in response to negative versus neutral stimuli was distinctly increased in the left amygdala and left hippocampus (but not in patients treated with unstated medications), was increased in the posterior cingulate cortex, and was blunted in the dorsolateral prefrontal cortex (dlPFC). Findings for GMV in BPD patients included smaller GMV in the right hippocampus; greater GMV in the right cerebellum and some right frontal regions; and, in unmedicated patients, smaller GMV in part of the inferior frontal gyrus.

Identifying Highly Vulnerable Children of Bipolar Parents

Joel Yager, MD reviewing Axelson D et al. Am J Psychiatry 2015 Mar 3.

Among children who eventually receive bipolar diagnoses, rates are elevated for prior subclinical mania/hypomania, disruptive behavior, ADHD, anxiety disorders, and substance abuse.

Because genetic contributions to bipolar disorder are prominent, children of bipolar parents are especially vulnerable to mood and anxiety disorders. Families and clinicians are eager to identify those particularly at risk as early as possible. These investigators followed 391 school-age children of 236 bipolar parents (bipolar I, 170; bipolar II, 66) and 248 offspring of 141 community-based parents. Mean follow-up was 7 years, with a mean of 2.7 assessments (initial mean age, 12 years). Parents in the bipolar group compared with the community group had higher rates of comorbid major depression, anxiety disorders, attention deficit/hyperactivity disorder (ADHD), and disruptive behavior and substance use disorders; their co-parents had higher rates of depression and substance use disorders. At the final assessment, children in the bipolar group had higher lifetime rates of psychiatric illness than children in the comparison group:

- Axis I disorders: 74% vs. 48%
- Mood disorders: 48% vs. 22%
- Any bipolar spectrum disorder: 19% vs. 2%

Among the 75 high-risk offspring with bipolar diagnoses, 15 had bipolar I, 18 had bipolar II, and 42 had bipolar disorder not otherwise specified. Fifteen high-risk offspring had manic episodes — 8 before age 12, the earliest at age 8. Before the first manic or hypomanic episode (n=36), 56% experienced a major depressive episode, and 36% had a subthreshold manic or hypomanic episode. Elevated risks for mania/hypomania were associated with ADHD and disruptive behavior disorders. In sensitivity analyses, only subthreshold mania/hypomania was associated with prospectively observed mania/hypomania.

Sleep Therapies May Also Make You Healthier

Steven Dubovsky, MD reviewing Irwin MR et al. Biol Psychiatry 2015 Feb 4.

Even when improvements in sleep were not maintained, inflammation levels continued to be lower.

Insomnia is associated with increased inflammation and its consequences, such as depression and various medical illnesses. These investigators examined inflammation levels in 123 older individuals (mean age, 66) with chronic insomnia participating in a randomized study of two nonpharmacological insomnia therapies.

The treatments were 4 months of twice-weekly cognitive-behavioral therapy (CBT-I), which targets sleep behaviors and arousal, and tai chi chih (TCC), which emphasizes relaxation and is associated with reduced sympathetic nervous system activity. A control condition provided educational sessions about sleep hygiene. The two active treatments were associated with improved sleep. With CBT-I, this improvement was maintained for a year after the intervention

(i.e., month 16), whereas with TCC, it waned over time, possibly because participants spent less time practicing.

Compared with the control, CBT-I reduced systemic inflammation, as measured by C-reactive protein, as well as pro-inflammatory gene expression. TCC reduced cellular inflammation and pro-inflammatory gene expression. Exercise levels and body-mass index did not change in any group.

Outcome of Cerebral Malaria

Robert S. Baltimore, MD reviewing Seydel KB et al. N Engl J Med 2015 Mar 19.

Death associated with cerebral malaria appears to be due to cerebral edema caused by sequestration of parasites within the cerebral microvasculature.

In Africa, case fatality rates among children with cerebral malaria (CM) remain high — 15% to 25% — despite effective antimalarial drugs. To determine the pathogenesis of this condition and the risk factors for death from it, investigators studied children aged >5 months who were treated for CM at a single hospital in Malawi between January 2009 and June 2011.

All 168 children had decreased consciousness and ophthalmologist-diagnosed malarial retinopathy. All underwent magnetic resonance imaging (MRI) on admission and ocular funduscopy within 6 hours after admission, and all were treated with intravenous quinine. Mechanical ventilation was not available.

Severely increased brain volume was more likely in the 25 children who died than in the 143 who survived (84% vs. 27%; $P < 0.001$). Brain swelling was most notable in the postpontine and prepontine areas, where the cerebrospinal fluid volume was significantly decreased. The 21 children with severely increased brain volume who died all had respiratory arrest, consistent with the effects of increased intracranial pressure. Thirty-five children had repeat MRIs; brain swelling was further increased in the 5 who died but not in the 30 who survived.

Personalized Medicine and Psychiatry: Dream or Reality?

Psychiatric Times

Uzoezi Ozomaro, MD, PhD

Charles B. Nemeroff, MD, PhD

Claes Wahlestedt, MD, PhD

CME | October 09, 2013 | Major Depressive Disorder, CME, Cultural

Psychiatry, Neuropsychiatry, Psychopharmacology

By Uzoezi Ozomaro, MD, PhD, Charles B. Nemeroff, MD, PhD, and Claes Wahlestedt, MD, PhD

This article explores the current state of knowledge regarding personalized medicine in psychiatry and discusses how the tools might be used to help psychiatrists understand the components of their patients' unique endophenotypic profiles.

CME credit for this article is now expired. It appears here for informational purposes. Some of the material may have changed.

Premiere Date: October 20, 2013

CME Expiration Date: October 20, 2014

Article Goal

The goal of this activity is to present information on personalized medicine and how it may be used to guide the decision making process in psychiatry.

Learning Objectives

At the end of this article, readers should be able to:

1. Identify the factors that make up a patient's physiological psychiatric profile.
2. Recognize the role of genetics, environment, and epigenetics in personal medicine.
3. Describe how clinical phenotype can be used to more clearly identify a diagnosis.

Target Audience

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

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Dr Ozomaro has received grant support from the National Institutes of Health/National Institute of Mental Health.

Dr Nemeroff is a consultant for Xhale, Takeda, SK Pharma, Lundbeck, Shire, Roche, Eli Lilly, and Allergan; has received grant/support from the National Institutes of Health, Agency for Healthcare Research and Quality; is a stock shareholder of CeNeRx BioPharma, PharmaNeuroBoost, Reevax Pharma, Xhale, and NovaDel Pharma; is or has been on the Board of Directors of American Foundation for Suicide Prevention (AFSP), Mt Cook Pharma (2010), NovaDel Pharma (2011), Skyland Trail, Gratitude America, and Anxiety and Depression Association of America (ADAA); sat on the Scientific Advisory Board for AFSP, CeNeRx BioPharma, National Alliance for Research on Schizophrenia and Depression, Xhale, PharmaNeuroBoost, ADAA, Skyland Trail, and AstraZeneca Pharmaceuticals (2009); holds a patent for method and devices for transdermal delivery of lithium (US 6,375,990B1) and for a method of assessing antidepressant drug therapy via transport inhibition of monoamine neurotransmitters by ex vivo assay (US 7,148,027B2); and has equity or other financial interests

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Dream or reality: to be fair, personalized medicine in psychiatry in its current state is best described as a dream not yet realized. We're closer than ever before, although to say there are many examples of personalized medicine in psychiatry would be an overstatement. However, we are at an exciting time, when a paradigm shift is occurring: we can begin to factor in data beyond the constellation of symptoms described or exhibited by our patient, and make better educated decisions for his or her clinical care. In fact, the reservoir from which we draw our patient information is growing exponentially—from the traditional self-report to genetics, neuroimaging, and environmental exposures. In the challenging field of psychiatry, we are not yet at the same level of understanding as in, notably, oncology, where there are highly personalized treatments based on molecular diagnostic testing.

This article explores the current state of knowledge regarding personalized medicine in psychiatry and discusses how the tools might be used to help psychiatrists understand the components of their patients' unique endophenotypic profiles. How psychiatrists can leverage neuroimaging and genetics to personalize their patients' care is also discussed.

Personalized medicine and what it means for psychiatry

Personalized medicine centers on the principle that by integrating data from a person's genetic makeup, epigenetic modifications, clinical symptoms, biomarker changes, and environmental exposures, we can achieve greater accuracy in diagnosis, prediction of disease susceptibility, and ultimately, therapy targeted to the individual.

Personalized medicine is certainly not a new concept, although it has been considerably more visible since the completion of the Human Genome Project and associated efforts. Personalization of medicine is best exemplified in oncology, which, for example, has had successes with the selective use of genetic testing of breast cancer susceptibility genes (BRCA 1, BRCA 2) to guide the clinical decision-making process.

Few examples of personalized medicine exist in psychiatry, because of a host of factors, such as complicated inheritance patterns, reliance on subjective self-report, and clinical heterogeneity of disease. However, the potential for personalized medicine to revolutionize psychiatry is quite pronounced. As an example, consider MDD: more than 10% of the population older than 12 years

report taking antidepressants, and remission rates achieved with current antidepressants are unacceptably low, while the morbidity and mortality of poor treatment or no treatment are exceedingly high. Even a small improvement in the odds of remission would likely have a large public health benefit, improve patient outcomes, reduce suicide rates, and increase treatment compliance and patient and physician satisfaction.

Interpreting a patient's physiological psychiatric profile

An initial challenge in personalized medicine in psychiatry is identifying useful information. One way of conceptualizing the patient for whom individualized care is needed is to acknowledge that each person has a unique phenotypic profile capable of informing clinical decisions. Some proposed categories include genetics, epigenetics, environment, biomarkers, and clinical phenotype. Each category has the propensity to help zero in on the ideal care for the patient, although the greatest benefits will surely be achieved when factoring in components from multiple categories.

Genetics

One expectation of personalized medicine is that susceptibility or protective factors mediated by genetic change can be determined. Other expectations are that genetic data can guide drug development and that treatment outcome can be predicted. It is important to note that even in the era of genome-wide association studies, the majority of these replicable genetic findings do not pinpoint the common genes that underlie disease; instead, our understanding centers around rare genetic variants that account for relatively small percentages of heritability. Nonetheless, certain influential findings deepen our understanding of major psychiatric illnesses and have introduced possibilities for predicting susceptibilities and targeting therapy via pharmacogenomics.

For example, ethnic differences in the alcohol dehydrogenase (ADH) and the mitochondrial aldehyde dehydrogenase (ALDH2) enzymes may underlie susceptibility to alcohol dependence. The ADH enzyme is encoded by a polygene family that includes ADH1B. The typical ADH1B isoform is found in approximately 95% of whites, while the atypical ADH1B isoform is found in 90% of Pacific Rim Asian ethnic groups, and it demonstrates much more rapid alcohol metabolism than the typical isoform. A similar relationship exists for ALDH2: ALDH2 has predominantly 2 major isozymes, one that is common in many ethnic groups (ALDH2*1), and the other (ALDH2*2) that is catalytically inactive and more prevalent in Pacific Rim Asians. Both isozymes that are more common in Asians, atypical ADH1B and ALDH2*2, have been associated with acute alcohol sensitivity and with protection against alcoholism. The ALDH2*1 isozyme, on the other hand, is more common in non-Asian populations and has a demonstrated association with alcoholism.

Environmental exposures and epigenetics

Some environmental exposures have been associated with psychiatric disease; for example, there is an 8-fold increase in the risk of schizophrenia in children whose mothers were diabetic during pregnancy. Environmental exposures likely underlie the perplexing finding that monozygotic twins are concordant for schizophrenia in only 45% of cases despite having identical DNA. Stress, especially early life trauma (child abuse and neglect), represents another environmental exposure linked to many psychiatric illnesses, most notably, mood disorders.

Epigenetics refers to gene regulation changes caused by mechanisms that do not involve nucleotide sequence modification. In many instances, epigenetic modifications have been demonstrated to occur after stress exposure.

CASE VIGNETTE

Jeremy is a 65-year-old man with chronic depression who, after years of being lost to follow-up, comes to the office for an initial psychiatric evaluation. A dozen trials with various antidepressants have failed. He reveals that his father died when he was 11 years old, and his mother remarried 2 years later. Jeremy suffered extensive physical abuse at the hands of his stepfather. He eventually dropped out of school and moved out at age 16.

Jeremy and his psychiatrist decided to change the treatment approach to a cognitively based analysis system of psychotherapy, consisting of elements from both interpersonal therapy and cognitive-behavioral therapy. Within 6 months, Jeremy's depressive symptoms were in remission. There is evidence of differential responses to antidepressant therapy and psychotherapy, which is contingent on the presence or absence of early life trauma. Patients who had experienced early life trauma responded significantly better to psychotherapy than to pharmacotherapy, while patients without early life trauma responded better to pharmacotherapy. An especially pronounced positive psychotherapy response rate was seen for patients who had experienced parental loss at a young age. Incorporating this environmental exposure into Jeremy's therapeutic plan helped achieve remission when previous interventions had failed.

Biomarkers and clinical phenotype

Biomarkers are characteristics that reflect biological function or dysfunction, response to a therapeutic measure, or indication of the natural progression of disease. Clinical phenotypes or endophenotypes are similar to biomarkers, but they do not require clinical manifestation of the disorder. These become most relevant when considering a patient who may not neatly fit into a diagnostic category. Grouping patients on the basis of heritable, consistent, clinical characteristics without regard to their strict nosological clinical diagnosis has the potential to broaden our clinical definition for certain illnesses and in some ways may be more likely to reflect a shared biological underpinning.

Electroencephalography is one modality that provides a reliable biomarker for characterizing epilepsy, and it has also been proposed to generate reliable biomarkers of psychiatric pathology. In fact, electroencephalographic (EEG) measures provided the foundation for the first FDA-approved medical device based on brain function to assess ADHD. Similarly, EEGs of patients with schizophrenia show consistent, replicable diminished amplitude of the P300 component of event-related potentials. Moreover, Mathalon and colleagues suggest that the characteristic reduction in event-related potentials amplitude can be used to differentiate schizophrenia from schizoaffective disorder.

One of the most rapidly developing subset of biomarkers leverages neuroimaging to develop quantitative biological phenotypes capable of characterizing or differentiating between psychiatric illnesses (Table). Some researchers are moving beyond merely characterizing psychiatric disease using neuroimaging, to monitoring the progression of treatment of such disease.

If we build in another layer of complexity by adding genetics to the equation, the burgeoning field of neuroimaging genetics is launched. This field harnesses genetics, psychiatry, and neuroscience to relate genetic variation to brain structure, function, and connectivity. The field is in a position to conduct experiments relating genetic profiles to outcomes of measurable, repeatable tests of brain structure and function. One example demonstrates the association between smaller hippocampal volumes and polymorphisms in the 5-HTT and BDNF genes.

The future of personalized medicine in psychiatry

Psychiatry has long been plagued by unacceptably low response rates to available treatments—both psychotherapeutic and pharmacological interventions—because trial and error often drive the

decision-making process. Having tools that aid the psychiatrist in identifying which patients are likely to respond to a particular treatment will surely improve patient outcomes and satisfaction. Although personalized medicine in psychiatry has progressed rapidly in the past decade, most of the findings are not ready for clinical application. Personalized medicine encourages clinicians to use all of the data at their disposal to provide the most effective care. Continued progress can be expected concomitant with our increasing comprehension and applicability of data and with studies that replicate and validate original findings.

What to do when a patient asks about personalized medicine

You may have a patient who asks, for example, "I heard that there is a new test for figuring out if a person has ADHD. Do you think I should take it?"

Keep in mind that such diagnostic tools are an adjunct to—and not a replacement for—sound clinical judgment. Ask yourself the following questions: Is this test appropriate for the patient? Is this likely to change the clinical management of the patient? If the answer to either of these questions is no, then there is no need to do the test—you would be doing a disservice to your patient. However, you could use these types of patient inquiries to fuel continuous learning during your practice. Also, you might encourage appropriate patients to enroll in clinical trials that are validating useful methods for personalization of psychiatric health care.

Disclosures:

Dr Ozomaro is a Resident Physician, Jackson Memorial Medical Center, University of Miami Leonard M. Miller School of Medicine, Miami. Dr Nemeroff is Chairman of the Department of Psychiatry and Behavioral Sciences, Director of the Center of Aging, and Chief of Psychiatry at Jackson Memorial Hospital and at the University of Miami Hospital at the Leonard M. Miller School of Medicine. Dr Wahlestedt is Associate Dean for Therapeutic Innovation, Leonard M. Miller Professor, Director of the Center for Therapeutic Innovation, and Vice Chair of Research for the Department of Psychiatry and Behavioral Sciences at the University of Miami Leonard M. Miller School of Medicine.

Medical Comorbidities in Late-Life Depression

Psychiatric Times

Abebaw Mengistu Yohannes, PhD

Robert C. Baldwin, MD

December 01, 2008 | Depression, Geriatric Psychiatry, Comorbidity In Psychiatry, Mood Disorders, Major Depressive Disorder

By Abebaw Mengistu Yohannes, PhD and Robert C. Baldwin, MD

Late-life depression is both underrecognized and undertreated, and the impact of medical comorbidity may mask depressive symptoms. Depression further complicates the prognosis of medical illness by increasing physical disability and decreasing motivation and adherence to prescribed medications and/or exercise or rehabilitation programs

The prevalence of depression is higher in persons with comorbid medical conditions than in those with no comorbidity. Some conditions that are common in older people, such as stroke, cardiac disease, chronic obstructive pulmonary disease (COPD), and diabetes mellitus, are associated with particularly high rates of depression comorbidity.

Late-life depression is both underrecognized and undertreated, and the impact of medical comorbidity may mask depressive symptoms. Depression further complicates the prognosis of medical illness by increasing physical disability and decreasing motivation and adherence to prescribed medications and/or exercise or rehabilitation programs. In addition, chronic disabling disorders can be a contributory factor to suicide attempts and completions in the elderly, but timely, appropriate treatment of depression can reduce this risk.

This review provides an update of current evidence in relation to late-life depression and its management in the presence of some common medical conditions: stroke, coronary heart disease, diabetes mellitus, Parkinson disease, and COPD. The relatively new concept of vascular depression is also briefly discussed.

STROKE AND MOOD DISORDER

Depression

Because depression and stroke are common in later life, poststroke depression is also common. Depression develops in 20% to 50% of patients within the first year after a stroke: the peak prevalence of major depression occurs at 3 to 6 months poststroke. However, the risk may continue for up to 2 or 3 years depending on the effects of disability on the patient's lifestyle. The variability in prevalence is probably the result of clinical heterogeneity of the sample, the timing of the evaluation, and the lack of a valid disease-specific screening questionnaire for poststroke depression.

A recent systematic review reported that the predisposing factors for poststroke depression include older age, a history of depressive disorder, the size of infarct, female sex, severity of stroke sequelae, and language impairment. Poststroke depression has been shown to be a predictor of impaired quality of life and a risk factor for cognitive decline and poorer functional recovery. It is also associated with an elevated risk of morbidity and mortality.

The literature is inconclusive about whether baseline depressive symptoms predict cerebrovascular events in older age. The Framingham Study examined the risk of developing cerebrovascular events in 2 cohorts of patients: one group was 65 years or younger and the other was older than 65 years.¹¹ The study used the Center for Epidemiologic Studies Depression (CES-D) score of greater than 16 as a cutoff for significant depression. Those 65 years and younger who had a CES-D score of 16 or greater were 4 times more likely to experience a stroke or transient ischemic attack as the same age-group without depression, after controlling for risk factors such as smoking status and education. There was no significant difference in the rate at which cerebrovascular events occurred in those who were 65 years or older, with or without depression.

In contrast, findings from another study indicate a positive association between the presence of depression and the risk of stroke across the entire adult age range. This study also demonstrated a gradient effect (the greater the depression, the greater the risk of stroke), which was most marked among black racial groups. The exact mechanisms of how depressive symptoms predispose to stroke are not fully known, but depression is known to affect autonomic function and platelet activation.

Diagnosing depression after a stroke can be difficult, especially in patients with aphasia. In their review of existing instruments, Bennett and Lincoln found the 14-item observer-rated Stroke Aphasic Depression Questionnaire Hospital Version (SADQ-H) to be effective. Difficulty in adjusting to major disability may be sufficient to trigger depression. However, the high rate of depression and the inconsistent relationship between severity of stroke and depression has led to a hypothesis based on the site of the lesion. It has been suggested that a stroke in the left front cerebral hemisphere is a major risk factor for depression, possibly caused by the interruption of

the monoaminergic routes that connect the brain stem with the cerebral cortex. However, other researchers disagree with the localization hypothesis.

Treatment

The principles of treating poststroke depression are the same as the treatment of depression in general. Because spontaneous recovery often occurs within the first 6 weeks, however, watchful waiting may be appropriate. The converse is also true—if a patient remains significantly depressed 6 weeks following a stroke, spontaneous remission is unlikely and somatic treatment should be considered.

A review of the literature provided information on only 10 randomized controlled trials of antidepressants (fluoxetine, citalopram, sertraline, nortriptyline) in poststroke depression. These drugs were shown to be efficacious, although the trials were small and of variable quality. Other antidepressants have been less well studied, although there have been controlled studies of psychostimulants such as methylphenidate at doses of 5 to 10 mg daily. Of historical interest, stimulants may also effectively target stroke-related apathy.

Antidepressants are preferred over psychotherapeutic interventions such as cognitive-behavioral therapy (CBT) because of a lack of evidence of efficacy of CBT. However, such trials are methodologically difficult to conduct. A recent study that examined the benefit of integrated care (liaison with a specialist stroke service, primary care physicians, using a telephone tracking system, management of vascular risk factors, and regular screening for depressive symptoms) in stroke survivors revealed fewer depressive symptoms in the integrated care group than in the control group in a 12-month follow-up. The integrated care approach has the potential for detecting and monitoring depressive symptoms in this patient population. It is hoped that future research will clarify the effects of both psychological approaches and stroke rehabilitation in the management of depressed mood.

CORONARY HEART DISEASE

There is a strong link between coronary heart disease and depression. In the United States, coronary heart disease affects more than 16 million people and in about 1 of 5 cases can lead to significant symptoms of depression. Nicholson and colleagues investigated the cause(s) and impact of depression as etiological and prognostic indicators in 54 observational studies. In 21 etiological studies the pooled relative risk (RR) of future coronary heart disease events in patients with depression was 1.81 (95% confidence interval [CI], 1.53 - 2.15)—patients with baseline depression were at 81% higher risk for coronary heart disease than patients without depression.

In 34 prognostic studies (among patient populations with an earlier myocardial infarction or coronary artery surgery), the RR of association of depression and prognosis for coronary heart disease was 1.80 (95% CI, 1.50 - 2.15). Of 804 Canadian patients with stable coronary disease, 7.1% met criteria for major depressive disorder and 5.3% for generalized anxiety disorder; both disorders increased the risk of subsequent adverse cardiac effects. This may be a conservative estimate. Depression in patients with acute coronary syndrome is less likely to be recognized (especially in ethnic minorities) in patients with lower educational backgrounds and reduced left ventricular ejection fractions.

Heart disease progression

The exact mechanism of the link between depression and coronary heart disease is unclear but includes direct biological mechanisms and behavioral factors. The Table lists the variables associated with depression and coronary heart disease.

The link between depression and coronary heart disease risk may be via autonomic dysfunction that manifests as reduced heart rate variability. Participants in 6 of the 13 studies that looked at depression as it relates to heart rate variability had coronary heart disease. Findings from those studies indicate that depression was associated with reduced heart rate variability. However, the effect sizes were too small to draw firm conclusions and there was much variation between the studies.

Inflammatory markers include C-reactive protein, interleukin-6, tumor necrosis factor, and fibrinogen. In a 2-year follow-up study, Frasure-Smith and colleagues investigated the relationship between depression and inflammatory markers. Elevated depressive symptoms and raised C-reactive protein levels 2 months after an acute event were overlapping risk factors for later cardiac events in men. Carney and colleagues demonstrated that fibrinogen was most highly associated with altered heart rate variability in depressed patients with coronary heart disease and proposed that this could be attributable to deficits in parasympathetic modulation of immunity and coagulation. In contrast, findings from the Heart and Soul Study suggest that major depression is associated with lower levels of C-reactive protein, fibrinogen, and interleukin-6. Differences in assessment scales and sample heterogeneity may have contributed to these disparate findings. Whatever the precise mechanism, untreated depression in cardiac patients is hazardous.

Treatment for depression

In the Sertraline Antidepressant Heart Attack Trial (SADHART), a study of 369 patients with a heart attack or unstable angina (mean age, 57), the SSRI sertraline was superior to placebo. Safety data were excellent. In the Enhancing Recovery in Coronary Heart Disease (ENRICH) study, patients with a recent history of heart attack (mean age, 61) benefited from cognitive therapy designed to modify negative thinking that may have contributed to their depression. Neither study showed improvement in cardiac outcomes, but there was a suggestion that larger trials might show that sertraline contributes to reduced mortality via its mechanism (shared by other SSRIs) of decreasing platelet activity.

Tricyclic antidepressants (TCAs) are type 1A antiarrhythmics that reduce heart rate variability, 2 factors linked to increased mortality. There is limited evidence on which to judge other antidepressants. Venlafaxine is known to raise blood pressure, although in older patients it can also lead to postural hypotension. It should not be used in patients with a high risk of ventricular arrhythmia. Therefore, the current recommended treatment for depression following an acute cardiac event or with stable heart disease is an SSRI.

DIABETES MELLITUS

As with heart disease, there is a 2-way interaction between depression and diabetes, although depression is only a modest risk factor for diabetes once lifestyle factors are accounted for. Other possible factors include activation of neuroendocrine pathways (leading, for example, to hypercortisolemia) and inflammatory responses that result in increased insulin resistance and the metabolic syndrome. In a large follow-up epidemiological study of middle-aged and elderly patients, those with incident type 2 diabetes were most likely to be depressed. This finding suggests that the impact of a new diagnosis is a significant factor for depression. It also suggests that early support might mitigate depression.

In patients aged 70 to 79 years there was a 30% increased risk of incident depression (odds ratio [OR], 1.31; 95% CI, 1.07 - 1.61), which was attenuated after adjustment for diabetes-related comorbidities (OR, 1.20; CI, 0.97 - 1.48); this still represents a significantly increased risk. Some studies suggest a link between depression and diabetic complications and poorer glycemic control. Painful neuropathy may be another causal factor. Diabetes can cause small-vessel

pathology in the brain that leads to subcortical encephalopathy, not unlike that seen in vascular depression. This may lead to both cognitive impairment and depressed mood.

TCAs are more likely to impair diabetic control than SSRIs. Fluoxetine should be used with caution, however, because as it can cause hypoglycemia. TCAs can be effective for painful neuropathy. Mirtazapine may cause weight gain (a risk factor for diabetes), lithium toxicity is increased if there is nephropathy, and valproate may give a false-positive result on urine testing for glucose.

There is increasing interest in alternative and complementary medicine to improve glycemic control and mood in diabetic patients, including Ayurvedic medicine, exercise, yoga, and acupuncture. There are also reports of the benefits of CBT. However, as with the treatment of depression in heart disease, it has yet to be demonstrated that such interventions actually are disease modifying (as measured by glycosylated hemoglobin levels).

PARKINSON DISEASE

Parkinson disease is characterized by slowness of movement, rigidity, resting tremor, shuffling gait, and postural instability. The reported prevalence of depressive symptoms varies widely from 7% to 76%, with an average of 40%. The cause of depression in Parkinson disease is multifactorial, but there is evidence linking it to neurodegeneration with an associated reduction in the neurotransmitter level not only of dopamine but other catecholamines important in mood regulation. However, 3,4-dihydroxy- l-phenylalanine (l-dopa) does not seem to improve mood in Parkinson disease patients. Serotonin and noradrenaline are probably more important.

In Parkinson disease with comorbid depression, there is more involvement of dopaminergic and noradrenergic pathways and reduced frontal metabolism than in Parkinson disease without depression. Other causal factors include social isolation, cognitive impairment, severity of disease, and duration of illness, although there is no consistent relationship between the last 2. Untreated depression in patients with Parkinson disease is associated with increased physical disability, impaired quality of life, and decreased social interaction. Ravina and colleagues found that more than 40% of their Parkinson disease patients had clinically significant depression that might benefit from intervention.

Treatment options for Parkinson disease with comorbid depression include antidepressants, electroconvulsive therapy, exercise, and CBT. Support groups and self-help programs are also encouraged.

Well-controlled clinical trials in the treatment of depression in Parkinson disease are scarce. SSRIs are most frequently prescribed. Although there are concerns that SSRIs can cause emergent extrapyramidal effects, this is controversial. The combination of an SSRI and selegiline can lead to the potentially fatal serotonin syndrome (altered level of consciousness, myoclonus, sweating, hyperreflexia, tremor, diarrhea, shivering, uncoordination, and fever). TCAs are not recommended because of anticholinergic effects. Tianeptine (which increases the presynaptic recapture of 5-hydroxyindole acetic acid) and moclobemide (a reversible and selective inhibitor of monoamine oxidase) have also been tried.

Evidence from a small study suggests that the use of the dopamine receptor agonist mirapex combined with l-dopa may improve not only motor activity, daily activities, quality of life, and dyskinesias but also anxiety and depression in patients with Parkinson disease. Modafinil, used to counteract sleepiness, has been used in Parkinson disease; in at least 1 antidepressant drug trial (not of Parkinson disease patients) it modestly diminished fatigue and sleepiness in patients with partially responsive SSRI-treated depression. Lastly, deep brain stimulation is a treatment for both

Parkinson disease and severe depression. To what extent this treatment may exert a specific antidepressant effect in patients with Parkinson disease is unknown, however.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

COPD is projected to be the third leading cause of death by 2020. A recent review of depression comorbid with COPD in the elderly identified a prevalence of 40% (95% CI, 36% - 44%). Untreated depression in patients with COPD is associated with increased physical disability, impaired quality of life, increased health care use, and increased mortality.

The mechanisms that link depression to patients with COPD is unclear. Possibilities include factors related to COPD (level of physical disability and fluctuating mood because of dyspnea), smoking (which increases the risk of vascular brain disease), and behavioral factors (lack of exercise, limited activity, and concomitant social isolation). Social factors are important and include the level of perceived and actual support and disruption to life caused by repeated hospital admissions (those with moderate to severe COPD are likely to have 3 or 4 admissions per year) or becoming housebound either through worsening disability or the need for continuous oxygen treatment.

There are no good trials of antidepressant medication in COPD but given the association of COPD depression with marked anxiety, a more sedating SSRI such as paroxetine or the non-SSRI mirtazapine can be tried. Benzodiazepines should be avoided because they depress respiration. Pulmonary rehabilitation based on activation and physical conditioning along with an antidepressant may be an effective approach compared with medication alone. Although there are limited data, in 1 study a 2-hour CBT session reduced both depression and anxiety. Furthermore, in a recent randomized controlled study, 8 weeks of group educational therapy was found to be as effective as CBT in alleviating depression and anxiety symptoms and improving quality of life in patients with COPD. It is worth replicating the findings of this study in other settings.

VASCULAR DEPRESSION

Vascular depression is a subgroup of late-onset depression symptoms that present with reduced depressive ideation, greater psychomotor disturbance, apathy, executive dysfunction (slow, inefficient thinking, difficulty in switching mental set), and neuroimaging abnormalities in the basal ganglia and white matter on MRI in older patients. It may account for 50% of newly diagnosed cases of major depressive disorder in later life. The cause of the structural brain changes is thought to be atheromatous damage to small penetrating arterioles deep within the brain. These vessels are end arteries and may be particularly susceptible to pulse-wave changes (pulse-wave encephalopathy) caused by factors such as arterial rigidity and/or hypertension. Many older adults have evidence of microvascular disease on brain imaging but not all of them have vascular depression or executive dysfunction. Hence, it is important to recognize the interplay of personal predisposition (from genetics or development), cognitive reserve, and cerebral lesion localization as well as overall lesion burden.

Standard antidepressant treatment is less effective in patients with microvascular disease than in nonvascular cases. One recent study demonstrated the benefits of augmenting fluoxetine treatment with nimodipine in patients with vascular depression. Nimodipine is a calcium channel drug used to lower blood pressure, and it may also dampen the systolic pulse wave to the brain. Such studies require replication but raise a question about what would be truly innovative depression-based treatment paradigms for halting vascular damage in those with vascular depression. For example, it is known that drugs such as statins, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers have vasoprotective properties that extend beyond their primary role. Until this research is carried out, it is as important to address vascular risk factors rigorously in late-onset depression as it is to treat depression.

Another approach is to target symptoms, such as apathy, linked to subcortical brain disease and hence vascular depression. No trials have been undertaken, but it has been suggested that dopamine-acting agents may be effective in depressed patients with frontostriatal impairment that leads to low motivation. In addition, antidepressants and other psychotropic agents with α -blocking action may inhibit behavioral recovery following ischemic lesions, whereas psychotropic drugs that increase catecholaminergic activity may promote recovery. Such concepts may guide future treatment. Low motivation or apathy has been treated with problem-solving treatment and behavioral activation with some encouraging results.

CONCLUSION

Several medical conditions that are prevalent in later life are associated with increased rates of depression. The extent to which the link is biological is debatable because, particularly in older people, the causes of depression are multifactorial. There is increasing evidence that depression itself is associated with the development of several diseases, especially those that involve the blood vessels. It is interesting to see if future research is able to identify whether vasoprotective drugs can improve the prognosis for vascular depression.

There is every reason to be optimistic about treating depression in older adults with medical comorbidity. There are effective psychological and antidepressant drug treatments, both for the immediate management and to keep the patient well after recovery from depression.

Food-Drug Interactions in Psychiatry: What Clinicians Need to Know

Psychiatric Times

Christina S. Won, PharmD, PhD

CME | June 19, 2014 | CME, Psychopharmacology

By Christina S. Won, PharmD, PhD

This review focuses on clinically important interactions that occur between foods and medications prescribed for psychiatric disorders.

Premiere Date: June 20, 2014

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This activity offers CE credits for:

1. Physicians (CME)
2. Other

ACTIVITY GOAL

This article reviews clinically important interactions that occur between foods and medications prescribed for psychiatric disorders, with a focus on underlying mechanisms.

LEARNING OBJECTIVES

At the end of this CE activity, participants should be able to:

1. Understand the mechanisms underlying food-drug interactions.
2. Define the basis for altered pharmacokinetics and pharmacodynamics.
3. Identify the role of metabolism in food-drug interactions.

TARGET AUDIENCE

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

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The act of food consumption is integral to the body's response to foreign substances, such as environmental toxins and pharmacological agents. Diet has the greatest opportunity to affect drug disposition, since most drugs and foods enter the body via the oral route and are subject to the same (sometimes competing) processes of absorption, distribution, metabolism, and excretion. The likelihood and magnitude of an interaction depends on several variables: physicochemical properties of a drug (ie, pH, solubility); food composition and timing; postprandial changes in the GI tract, and patient characteristics (eg, dietary habits, nutrition status). This review focuses on clinically important interactions that occur between foods and medications prescribed for psychiatric disorders. Underlying mechanisms, examples, and clinical recommendations are presented.

Food-drug interactions can manifest as altered pharmacokinetics (PK) and/or pharmacodynamics (PD) of a drug. Drug absorption, distribution, and elimination may be enhanced or inhibited by food, which can lead to decreased or increased systemic drug concentration. Food can also interfere with a drug's binding to its receptor, leading to decreased or increased effectiveness. Psychotropic agents can exert serious adverse effects (eg, profound sedation, hypertensive crisis, QTc prolongation) as well as potentially devastating behavioral outcomes due to decreased or lack of therapeutic effectiveness.

The effects of food

Potential clinical significance of food-drug interactions is recognized by regulatory agencies, each with specific guidelines. In 2002, the FDA released a guidance for the design and conduct of studies on the effects of food as well as the effects of fasted vs fed states. According to the FDA, high-calorie (approximately 800 to 1000 calories) and high-fat (approximately 50% of total caloric content) meals are more likely to produce the greatest adverse effects on GI physiology and subsequent systemic drug availability.

On the basis of the magnitude of change in systemic drug exposure (area under the concentration curve [AUC]), maximum drug concentration (C_{max}), and/or time to C_{max} (t_{max}), compared with fasting conditions, a drug can be "taken with or without food." Food marginally increases quetiapine C_{max} and AUC by 25% and 15%, respectively. Therefore, quetiapine can be taken with or without food. In contrast, a food effect study in 30 healthy male volunteers given zolpidem while fasting or 20 minutes after a meal showed that food decreased mean C_{max} and AUC by 15% and 25%, respectively, and increased t_{max} by 60% (1.4 to 2.2 hours). Because of the potential for delayed onset of sleep, zolpidem is not to be taken with or immediately after a meal.

For some drugs, the clinical implication of a food effect is unknown. Diazepam absorption was decreased and delayed by approximately 30 minutes when administered with a moderate-fat meal compared with fasting: t_{max} was increased by 1.25 hours; C_{max} and AUC were decreased, on average, by 20% and 27%, respectively; however, the label does not provide a recommendation.⁷ Table 1 lists psychotropic agents with explicit instructions on drug and food intake as specified in the package insert.

Mechanisms of altered drug exposure and response

An understanding of the various effects of food and/or food components on drug behavior is the basis for optimizing therapy. Interference from a food or food component depends on numerous variables, ranging from physicochemical properties of the drug to physiological changes in the GI tract after a meal. Components of the diet that modulate drug-metabolizing enzymes (eg, cytochrome P-450 [CYP450] enzymes, phase II conjugation enzymes) and transport proteins (eg, P-glycoprotein) are increasingly recognized as contributors to food effects on drug disposition.

Changes in these physiological, physicochemical, and biochemical interactions can be evaluated using drug PK measures such as clearance, systemic exposure/AUC, C_{max} , t_{max} , and bioavailability. It is important to note that such measures are clinically relevant if patient response (or nutrition status) is compromised. An increase in systemic drug exposure may augment the risk of adverse events and toxicity; a decrease in exposure may lead to therapeutic failure. Despite the lack of an established PK-PD relationship, clinicians should not discount the relevance of a theoretical food-drug interaction, especially for drugs with a narrow therapeutic index (ie, lithium, carbamazepine, phenytoin).

Absorption

The GI tract poses a formidable barrier to successful delivery of an orally administered drug to the site of action. However, chelation is a more fundamental obstacle to absorption. Binding between

the drug and food is a physicochemical interaction that can lead to decreased absorption. For example, proteins and salts in enteral nutrition formulas bind to phenytoin, resulting in reduced absorption. Although irrelevant to psychotropic therapies, a noteworthy classic example is the complexation of foods containing divalent cations (eg, calcium, magnesium) and drugs such as levothyroxine, tetracyclines, and fluoroquinolones. In contrast, high-fat meals can increase bioavailability of some drugs, such as the antiretroviral protease inhibitors nelfinavir and saquinavir.

It is interesting to note that ziprasidone and lurasidone are the only psychiatric medications with specific calorie requirements to aid absorption. The precise mechanism is still unknown. The package insert for ziprasidone recommends concomitant intake with food, which provides an up to 2-fold increase in absorption. More specifically, a clinical trial that evaluated the effects of different caloric and fat content on ziprasidone systemic exposure showed that a meal with 500 kcal or more (irrespective of fat content) is required for optimal bioavailability.

The package insert for lurasidone recommends concomitant intake with 350 kcal or more, because lurasidone C_{max} and AUC are increased approximately 3- and 2-fold, respectively, compared with fasting conditions. (Lurasidone exposure was not affected as calorie content was increased from 350 to 1000 kcal and was independent of meal fat content.)

Food and/or food components can alter the rate and extent of drug absorption by affecting physiological processes and/or "mechanics" of the GI tract. Such mechanisms include delayed gastric emptying, increased bile or splanchnic blood flow, and gastric pH changes. For example: amphetamines are well absorbed under alkaline conditions; acidic foods and beverages such as fruit juices and soft drinks may decrease gastric pH and subsequent amphetamine absorption.

Distribution

Drug molecules can bind to plasma proteins such as albumin and α 1-acid glycoprotein, depending on physicochemical properties and the amount of plasma proteins in the patient's blood (which can be influenced by nutrition status). Highly protein-bound psychotropic agents (more than 95%), such as valproic acid, antipsychotics, and SSRIs, are susceptible to displacement by other drugs and nutrients binding to the same site(s). However, clinically significant food-drug (and drug-drug) interactions due to plasma protein binding are rare. A suspected interaction should be confirmed with therapeutic drug monitoring (ie, free drug level).

Metabolism

The CYP450 family is the predominant group of phase I enzymes involved in drug metabolism. Psychotropic medications are typically metabolized by one or more of the following isoforms: 3A4, 2D6, 2C8/9/19, 2B6, and 1A2. Certain foods and specific dietary substances can inhibit or induce these CYP isoforms, leading to increased or decreased systemic drug exposure. Clinical significance of these interactions depends on several factors, including metabolic contribution of specific CYP isoforms, amount and frequency of dietary substance, site (intestine and/or liver), and timing.

Few foods are capable of clinically significant CYP induction. Char-grilled meat and broccoli (consumed for longer than 5 days) have been shown to induce CYP1A2 activity, as demonstrated by increased metabolism of caffeine (ie, CYP1A probe). Clozapine, olanzapine, and duloxetine are partially metabolized by CYP1A2; an interaction with the aforementioned foods would result in decreased drug exposure. However, no formal studies on this theoretical interaction have been reported.

Grapefruit juice has been shown to inhibit the metabolism of various CYP3A substrates. It can be a strong or moderate inhibitor of CYP3A-mediated first-pass metabolism in the intestine. Although

inhibition is localized in the intestine, increased systemic drug exposure is sufficient to produce adverse effects, such as excessive sedation with buspirone and diazepam. Some CYP3A substrates (eg, clozapine, alprazolam, haloperidol) have not been shown to be affected by grapefruit juice. However, lack of an observed interaction may be attributed to insufficient or no analysis of the causative inhibitory constituents, one of the most important factors to consider. Since the majority of grapefruit juice–drug interaction studies do not report furanocoumarin content, it is difficult to reconcile conflicting results or compare between studies.

Excretion

Food and nutrients may act to alter drug reabsorption by renal tubules and excretion in urine. For example, lithium is a monovalent ion like sodium, and it is excreted unchanged primarily in urine. Since the kidneys do not distinguish between the two ions, large fluctuations in dietary sodium can change lithium concentration. Lithium decreases sodium reabsorption by the proximal tubule, leading to sodium depletion. Reduced sodium intake can lead to lithium reabsorption, whereas increased sodium consumption can increase lithium excretion. Patients should be advised to maintain consistent salt and caffeine intake as well as adequate hydration (2.5 to 3.5 L) during the initial stabilization period.

PD-based food-drug interactions occur when food modifies the effect of a drug. Certain food components can enhance or antagonize pharmacological actions at the site(s) of action (eg, receptor) or other mechanisms in the same tissue. Changes in PD end points can be evaluated using qualitative (eg, symptom score, vital signs) and/or quantitative (eg, biomarker levels) measures that may be primary or surrogate indicators of drug action.

Wine, beer, and distilled liquor are CNS depressants, and concomitant intake is not recommended because of additive effects for drowsiness, dizziness, and impaired cognition. Caffeine, on the other hand, is a stimulant, and excessive intake can potentiate drug adverse effects such as tachycardia, anxiety, restlessness, and tremor.

The most well-known PD-based interaction occurs between MAOIs and tyramine. Tyramine is a monoamine produced by MAO-mediated metabolism of tyrosine in some foods. In addition to tyramine, MAO breaks down neurotransmitters such as dopamine, norepinephrine, and serotonin. Inhibition of MAO by certain antidepressants and unrestricted consumption of tyramine can lead to severe hypertension, arrhythmia, and headache. Many foods were originally contraindicated, but recent data suggest a less restricted list of foods to be avoided (Table 2).

Patients should be warned that tyramine content may vary, and levels increase when foods are aged or fermented, are stored for a long time (even in a refrigerator), or are not fresh. Given these variables and the erratic GI absorption of tyramine, lack of a serious reaction from (accidental) consumption of a restricted food on one occasion is not guaranteed on a different occasion.

Nutraceuticals

Although investigation of the "food effect" on drug exposure is standard practice, the issue may not be as simple as "take with or without food." Specific dietary supplements and herbs have been shown to alter drug PK and PD. These interactions are challenging to assess because, unlike most drug products, dietary and herbal substances are compounds, composed of multiple, and usually unknown, bioactive ingredients. Use of such products as adjuncts to prescribed medication(s) has increased over the past decade, although concomitant therapy is not recommended.

Special populations

The interaction between food, nutrients, and drugs can be difficult to discern in terms of the precise effects of these relationships in the body. Added complexity from immature, aging, or pregnant physiologies creates added uncertainty. Drug-drug interactions for specific populations may be

addressed in the package insert and specialized guides. However, food-drug interaction research in these vulnerable populations is sparse.

Conclusion

The risk of food-drug interactions is expected to increase with the rising trend of polypharmacy and the diverse food products/ingredients available on the market. Some interactions may be avoided simply by separation of drug administration and food intake (by minutes or hours) or manipulation of the dosage form (eg, delayed-release, enteric coating). Other strategies may be applied depending on each patient situation. The following are general recommendations:

- Read the package insert or patient counseling pamphlet for instructions on dose administration
- Titrate doses and administration time(s) relative to meals and meal composition
- Advise patients to inform prescriber(s) if significant changes in the diet are planned or have occurred before or during therapy initiation or titration (some medications suppress or stimulate appetite as a mechanism of action or adverse effect)
- Exercise caution when interpreting results from drug interaction–checking software, which may overreport

An Imaging Biomarker for Migraine?

Neurology Times

Thomas P. Bravo, MD

Bert B. Vargas, MD

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By Thomas P. Bravo, MD and Bert B. Vargas, MD

Intriguing research is helping to shape our understanding of the functional connectivity and brain structure of migraineurs.

At a plenary session at AAN2015, Todd Schwedt, MD, presented intriguing research that is helping to shape our understanding of the functional connectivity and brain structure of migraineurs.

We know that migraineurs demonstrate abnormal sensory processing—including abnormal pain integration, modulation, and affective processing. Even between attacks, migraineurs exhibit increased sensitivity to light, sound, and smell. They also have increased rates of pain disorders that may have altered central processing, such as irritable bowel syndrome and fibromyalgia. This suggests that abnormal sensory processing in migraine is potentially the result of altered brain function.

Recent research using resting state functional connectivity MRI supports the presence of abnormal functional connections in those with chronic migraine. Functional connections between the anterior insula, amygdala, pulvinar, mediodorsal thalamus, middle temporal cortex, and periaqueductal gray have been described: functional connections between the anterior insula and both the mediodorsal thalamus and periaqueductal gray specifically correlate with the length of time a person has experienced chronic migraine. Dr Schwedt presented additional research which demonstrated abnormal functional connectivity in these areas, as well as evidence that cortical thickness of the temporal parietal junction region may be abnormal.

A study compared 31 adults with episodic migraine with 32 healthy controls utilizing quantitative sensory testing (QST) and regional cortical thickness using 3 Tesla MRI. Each subject's heat pain

threshold was quantified at the left forearm using QST. Cortical thickness was measured next using T1-weighted sequences by general linear model whole-brain vertex-wise analysis. Subjects were grouped by pain threshold and those with migraine were then compared to controls.

Healthy controls with low heat pain thresholds had a thicker cortex in left superior temporal/inferior parietal region. Migraineurs with low pain heat thresholds had thinner cortex in this area ($P < .01$). There was no change in this area among the migraineur group despite disease-varied severity, which suggests that this may be an underlying trait of those with migraine. This region is involved in the cognitive aspect of pain, specifically directing attention toward or away from environmental or painful stimuli. One could hypothesize that having this trait may explain why someone with migraine may have a difficult time distracting himself or herself from pain and other nonpainful stimuli.

Take home points

The potential implications of this research may lead us to an imaging biomarker for migraine using volume, surface area, and thickness of specified brain regions on standard MRI. While migraine remains a clinical diagnosis, structural imaging may eventually become a helpful adjunctive clinical tool.

A Novel Acute Migraine Treatment

Neurology Times

Thomas P. Bravo, MD

Bert B. Vargas, MD

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By Thomas P. Bravo, MD and Bert B. Vargas, MD

A novel drug-device may not only be a promising non-oral triptan acute migraine treatment, but may be more efficacious than its oral counterpart.



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Attendees at the AAN 2015 conference got a look at a novel drug-device for acute migraine treatment. AVP-825 is a breath-powered intranasal delivery system of lower-dose powdered sumatriptan. This drug-device combination is designed as a potential non-oral treatment option with the goal of faster and more effective systemic absorption and pain relief without the need for injection.

A meta-analysis of the pooled results of phase 2 and phase 3 clinical trials of AVP-825 was presented, which demonstrated efficacy in a cohort of patients with episodic migraine without either sumatriptan or 2 or more triptan failures and with normal palate and nasal function. Beginning at 30 minutes, significant pain relief occurred compared with placebo (44.8% vs 27.9%). Pain freedom at 2 hours was noted in 40% compared with 19.21% in the placebo group. 46.9% of treated patients reported no clinical disability at 2 hours vs 27.9% in the placebo group ($P < .01$). No significant adverse events were noted: 1 patient reported paresthesias; 20% noted abnormal taste; and 11% reported mild nasal discomfort.

Overall this meta-analysis is consistent with the prior phase 2 and 3 clinical trials, which demonstrated efficacy of AVP-825 as a non-oral acute migraine treatment option.

This poster session comes as a precursor to the presentation of data from the COMPASS study (Breath Powered Nasal Delivery of 22 mg Sumatriptan Powder (AVP-825) Versus 100-mg Oral Sumatriptan in Acute Migraine: A Comparative Clinical Trial). This is a recently completed multicenter, double-dummy, crossover, 12-week study that compares AVP-825, 100-mg oral sumatriptan, and placebo for acute migraine treatment. COMPASS demonstrated that for 2 or more attacks, AVP-825 was superior to oral sumatriptan at 30 minutes pain relief (37.6% vs 18.8%, $P < .0001$) and 30 minutes pain freedom (15.7% vs 6.4%, $P = .015$).

Overall, this study suggests that AVP-825 may not only be a promising non-oral triptan acute treatment, but may be more efficacious than its oral counterpart.

Parenting to Prevent Narcissism and Develop Self-Esteem

Martin T. Stein, MD reviewing Brummelman E et al. Proc Natl Acad Sci U S A 2015 Mar 9.

Parental overvaluation was associated with child narcissism; parental warmth was associated with self-esteem.

Narcissism — a grandiose view of one's own talents and a craving for admiration — is a personality trait that may restrict normal development. To understand factors that predispose children to narcissism during late childhood, when narcissistic traits emerge, investigators conducted a prospective, longitudinal study of 565 Dutch children (7–11 years old) and their parents.

Children completed standardized questionnaires to assess narcissism (e.g., “kids like me deserve something extra”), self-esteem (e.g., “kids like me are happy with themselves as a person”), and parental warmth (e.g., “my father/mother lets me know he/she loves me”). Parents completed standardized questionnaires to assess parental overvaluation (e.g., “my child is more special than other children”) and parental warmth (e.g., “I let my child know I love him/her”). The questionnaires were administered every 6 months during an 18-month period.

Overvaluation by a mother or a father was significantly associated with child narcissism but not with self-esteem. Child-reported and parent-reported parental warmth was not associated with child narcissism but was associated with self-esteem. The authors suggest that children develop narcissism by internalizing parents' inflated views of them (e.g., “I am superior to others,” and “I am entitled to privileges”).

Clinical Issues and Strategies Associated With Smoking Cessation

Psychiatric Times

Stephen E. Hall, MD

Judith J. Prochaska, PhD, MPH

March 20, 2015 | CME, Addiction

By Stephen E. Hall, MD and Judith J. Prochaska, PhD, MPH

Here: assessment approaches, treatment options, and potential risks inherent in treating tobacco dependence in individuals with major mental illnesses and substance use disorders.

Premiere Date: March 20, 2015

Expiration Date: March 20, 2016

This activity offers CE credits for:

1. Physicians (CME)

2. Other

ACTIVITY GOAL

To understand the obstacles standing in the way of smoking cessation in patients with mental illness and the strategies that can help patients abstain from smoking.

LEARNING OBJECTIVES

At the end of this CE activity, participants should be able to:

1. Understand the obstacles that stand in the way of smoking cessation in patients with mental illness

2. Describe the recommendations of the US public Health Service and the American Psychiatric Association to help patients quit smoking

3. Describe the evidence base for treating tobacco addiction in smokers with co-occurring mental illness or addictive disorders

TARGET AUDIENCE

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

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Stephen E. Hall, MD, has no disclosures to report.

Judith J. Prochaska, PhD, MPH, reports that she has received an independent investigator award from Pfizer and is an ad hoc member of their advisory board and grant reviewer for their grant program. She has also served as an expert witness against the tobacco companies in several lawsuits for which she has received fees.

A. Eden Evins, MD, MPH (peer/content reviewer), has no disclosures to report.

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Tobacco smoking is the leading cause of preventable death in the US. Despite a steady decline in smoking in the general population since 1965, its prevalence among adults with mental health and substance use disorders remains high, with recent estimates from 50% to 85%, which currently represents about 16 million people. This group consumes about half of all cigarettes sold in the US and suffers a disproportionate share of medical burden, including cardiovascular and pulmonary diseases as well as cancer associated with smoking. Half of all smokers alive today will be killed prematurely by a disease linked directly to their tobacco use.

This article addresses issues inherent in treating tobacco dependence in individuals with major mental illnesses and substance use disorders, including assessment approaches, treatment options, and potential risks.

Obstacles and solutions

Although some advances have been made in addressing the persistently high rate of smoking in the mentally ill, these are limited mainly to the research environment. A variety of factors that contribute to the lack of focus on this dangerous health risk have been suggested. These include:

- A perceived reluctance to address smoking in the clinical practice setting
- Historical use of cigarettes as contingency rewards in institutions
- The marketing of cigarettes to those with mental illness
- Inconsistent insurance coverage for tobacco use treatment
- Other psychiatric or substance abuse problems get priority
- The belief that smoking is a form of "self-medication" for some patients
- Clinicians' fears that tobacco abstinence will cause decompensation of other conditions

- Lack of provider awareness, training, and education

Only half of US residency programs in psychiatry include training in the treatment of tobacco dependence. It is perceived that motivation to quit is low among smokers who have other substance abuse and mental health problems, but data suggest that this group is as interested in abstinence as is the general population.

Psychiatric inpatient hospitalization may be an especially fruitful time to mobilize interest in quitting and to initiate abstinence. In one recently published study of the efficacy of treatment for tobacco use on an inpatient service, measures of psychopathology did not predict abstinence, but measures of motivation and tobacco dependence did. Moreover, cessation treatment appeared to decrease the risk of rehospitalization, and the intervention was found to be highly cost-effective. Surveys of patients in substance abuse rehabilitation programs have found that the majority are motivated to quit, although a substantial number also express concern about their ability to quit tobacco and other substances simultaneously.

To overcome some of these obstacles, clinical and research leaders and policy advocates have proposed a systematic integration of tobacco dependence treatments into mental health programs. A successful example using this model is a large study from the Veterans Administration, which demonstrated that patients with PTSD and tobacco dependence who were treated for both disorders simultaneously had 2-fold greater quit rates than those who received care through referral to a smoking cessation clinic. Moreover, smoking cessation had no adverse effects on PTSD recovery. Because smoking so commonly co-occurs with mental illness, integrated psychiatric/ tobacco dependence treatment may be more cost-effective than the traditional split. In the approaching era of population-based systems of care, economic and clinical imperatives may hasten the adoption of such a model.

The US Public Health Service

The US Public Health Service update of 2008 provides an excellent guide to the assessment and treatment of tobacco use and dependence. These guidelines are for smokers in general, but serve as the basis for recommended approaches for smokers with comorbid psychiatric or substance use disorders. The individualized approach includes:

- A review of tobacco habits
- Advice to quit in clear and personalized terms
- Understanding specific health concerns
- Assessment of the individual's willingness to quit
- Assistance in forming a quit plan
- Creating follow-up actions

Clinicians can help patients move toward smoking cessation with motivational interviewing. This technique addresses specific content areas (relevance, risks, rewards, roadblocks, and repetition) and is associated with improved quit attempts.

Treatment options include referral to smoking cessation programs or the national telephone "quit line" (1-800-QUIT-NOW), practical counseling (eg, problem-solving/skills training), and medication support. Medications include nicotine replacement therapy (approved by the FDA in the form of patch, gum, lozenge, nasal spray, and inhaler), antidepressants (bupropion SR and nortriptyline), and an $\alpha 4\beta 2$ nicotinic receptor partial agonist (varenicline).

Monotherapy with varenicline has been shown to be more effective than other monotherapies and comparable to the combination of multiple forms of nicotine replacement (eg, patch plus gum or lozenge). In addition, the combination of nicotine replacement and bupropion SR has shown greater efficacy than either used alone.⁵ Case reports and postmarketing data raised concerns about

the risk of psychiatric adverse effects from both varenicline and bupropion SR, and in 2009, boxed warnings were added to labeling for both medications. Clinical trials data have not indicated a signal of concern, including in recent trials of varenicline use among smokers with current mental illness.

The American Psychiatric Association

In its practice guidelines for nicotine dependence and substance use disorders, the American Psychiatric Association recommends assessment of smoking status in all patients and assistance with quitting. The guidelines recommend use of motivational, behavioral, and pharmacological treatment; suggest using inpatient treatment as a good opportunity for initiating abstinence; and recommend nicotine replacement therapy for withdrawal symptoms. The guidelines note that with few exceptions, there is limited evidence for treatment interventions specific for smokers with particular psychiatric diagnoses.

Psychiatric comorbidity

Depression

Depression is twice as common in smokers as in nonsmokers, and 4 times as common in heavy smokers. Smokers with comorbid depression smoke more heavily than the average smoker, are more likely to relapse after an attempt to quit, and suffer greater physical morbidity and mortality than those in the general population. Prospective studies with adolescents and adults have implicated tobacco use as a predictor of future suicidal behavior. But some have expressed concern that past or currently depressed patients who quit smoking will lose a coping mechanism and decompensate.

Among patients with a history of depression, there are limited, discrepant data regarding the risk of smoking cessation. Findings from one prospective trial of sertraline for smoking cessation suggest that quitters had a higher rate of depressive relapse. However, a large percentage of continuing smokers were lost at follow-up, potentially underreporting depression recurrence in that group (sertraline itself was ineffective for abstinence).

In secondary analyses of 2 clinical tobacco treatment trials in smokers with a history of depression, smoking cessation did not increase rates of depressive symptoms or of major depressive relapses. Furthermore, in one of the only trials to test a cessation intervention among currently depressed smokers, quitting smoking, measured over 18 months, did not harm recovery from depression.

Nicotine withdrawal can produce some depressive symptoms for a 2- to 4-week period irrespective of depression history. Long-term effects, however, are encouraging: a recent meta-analysis found that smoking cessation is associated with reduced depression, anxiety, and stress and improved positive mood and quality of life compared with continuing to smoke, true for smokers with and without a history of depression.

Medications that are effective for tobacco cessation in smokers without mental illness have also shown similar effectiveness in patients with either current or prior depression. Bupropion SR does not have a differential effect on patients with a history of depression, as had once been hoped.

Varenicline more than doubled the odds of sustained tobacco abstinence compared with placebo for patients under stable treatment for current or past major depression, without exacerbating anxiety or depressive symptoms. In an analysis of data from the VA health care system that

compared varenicline with nicotine replacement therapy, no differences in rates of neuropsychiatric hospitalization were observed; findings were similar in the subsets of patients with and without a neuropsychiatric history who received either varenicline or a nicotine patch.

Schizophrenia

Rates of smoking in patients with schizophrenia are among the highest of any group. Combined with comorbid obesity and other metabolic disorders so common in this population, the results can be particularly deadly. Persons with serious mental illness die on average 25 years prematurely.

Only in recent years has there been an effort to address tobacco dependence in those with schizophrenic spectrum illnesses. Quit rates have been low, particularly with nicotine replacement therapy as the sole medication adjunct to psychological approaches. However, the combination of nicotine replacement therapy and behavioral counseling has been found to be effective (20% quit rate) in smokers hospitalized with schizophrenia, which was comparable to other diagnostic patient groups.

Concerns among clinicians that smoking cessation will exacerbate symptoms are not borne out by available data. In a trial that examined the use of bupropion for smoking cessation in schizophrenia, abstinence was not associated with worsened cognitive deficits or executive functioning. The combination of nicotine replacement therapy and bupropion was found more effective in 2 trials, with quit rates as high as 50% at the end of 12 weeks. However, relapse rates in both studies were high. Notably, there were no signals that abstinence or an attempt to quit worsened psychiatric symptoms.

More recently, varenicline was evaluated in a multicenter, randomized, controlled trial. Quit rates were 19% at 12 weeks and 11.9% at 24 weeks, with an odds ratio of about 5.0 relative to placebo. Varenicline was not associated with an exacerbation of schizophrenic symptoms or with changes in mood and anxiety ratings.

In a randomized placebo-controlled trial, extended use of varenicline (for 52 weeks) with CBT was found to prevent relapse among smokers with schizophrenia or bipolar disorder. From weeks 12 through 76, 30% of participants randomized to varenicline compared with 11% in the placebo group were continuously abstinent, with an odds ratio of 3.4. The CBT interventions focused on relapse prevention skills, such as understanding relapse, learning and applying skills, refusal skills, and problem solving.

A combination of social, psychological, and biological factors may lie behind the refractory nature of smoking among persons with schizophrenia. This population may be less aware of the associated health risks and feel that smoking is more important for their social functioning and acceptance. If noted during an evaluation, these factors could potentially be addressed in a personalized treatment plan. In general, heavy smokers have more difficulty in quitting, and persons with schizophrenia are generally heavy smokers.

Schizophrenia is characterized by deficits in executive planning as well as by resistance to change, so that even a motivated person may repeatedly lose focus on the goal of quitting cigarettes. Tobacco smoke (not nicotine) induces the metabolism of several antipsychotic medications (eg, olanzapine, haloperidol), which lowers blood levels and may reduce neurocognitive medication

adverse effects. Nicotine also may have a facilitative role in cognitive processes that are impaired in schizophrenia.³ Thus, it may make sense to include nicotine replacement therapy in the smoking cessation plan for any patient with schizophrenia and to consider varenicline ahead of other medication options.

Substance abuse

Traditionally, tobacco has not been included with other abused substances by rehabilitation programs as a target for abstinence. Perhaps because of its previously wide social acceptance and long-standing legal status, it has been relegated to a second-tier concern. However, evidence indicates that for some substance use disorders, continued smoking is associated with lower levels of sobriety from illicit drugs and alcohol.

A 2004 meta-analysis of 19 randomized controlled trials that evaluated tobacco cessation interventions with smokers in treatment or recovery for alcohol or illicit drug problems found significant posttreatment effects for quitting smoking, and nicotine replacement therapy was particularly helpful. Although tobacco cessation treatment effects were not maintained at long-term follow-up, notably there was a 25% improvement in long-term sobriety among those randomized to receive interventions for quitting smoking.

A large-scale study of treatment for alcohol dependence with tobacco cessation treatment administered either concurrently or with a 6-month delay, suggests that the timing of the two treatments may be important. At 18 months, subjects in the concurrent group were more likely than those in the delayed group to participate in smoking interventions, although at 18 months, abstinence rates in the two groups were similar. Alcohol abstinence rates were worse in the concurrent group at month 6, although not at months 12 and 18. Further research is needed to identify of the optimal timing of tobacco cessation interventions within addiction treatment settings, which may differ depending on the approach taken (eg, action-oriented "quit now" versus matched to stage of change or motivation).

Other disorders

Other major mental illnesses have received relatively little attention with regard to the treatment of comorbid tobacco dependence. Although adults with bipolar disorder are 2 to 3 times more likely to smoke, and less likely to stop than those without psychiatric disorders, this area has received little attention. In patients with anxiety disorders, there is a high prevalence of co-occurring tobacco dependence, but few studies have addressed treatment beyond the study of integrated tobacco cessation for smokers in treatment for PTSD in the VA health care system.

Conclusion

Treating tobacco dependence in smokers with mental health concerns is recommended as good clinical practice, is straightforward, and has demonstrated efficacy, without harm to mental health recovery. It is time to address the major health disparities related to tobacco use in this vulnerable population by providing evidence-based cessation treatment and referrals.

How Does Deep Brain Stimulation Work?

Steven Dubovsky, MD reviewing de Hemptinne C et al. Nat Neurosci 2015 May. Williams ZM. Nat Neurosci 2015 Apr 28.

It appears to affect cerebral rhythms across networks.

Deep brain stimulation (DBS) can improve Parkinson disease (PD) as well as psychiatric disorders such as major depression. To elucidate its mechanism of action, researchers examined subdural electrocorticography recordings obtained during implantation of DBS electrodes in the subthalamic nucleus (STN), and afterwards, in 23 PD patients.

At baseline, low-frequency activity (13–30 Hz; beta band) in the STN was strongly correlated with fast activity (50–200 Hz; broadband gamma) in the motor cortex, a phenomenon known as phase-amplitude coupling (PAC). Active DBS attenuated PAC when patients were at rest and during preparation to move, movement toward a target, and touching the target. After the stimulus was turned off, PAC returned to the baseline state only in patients who had exhibited reduced rigidity with active DBS.

It's All in the Family: Children's Parasomnias Are Often Familial, Decrease over Time

Barbara Geller, MD reviewing Petit D et al. JAMA Pediatr 2015 May 4.

Reassuring data from longitudinal analyses of a Quebec population

Although clinicians and many families are aware of the familial nature of parasomnias, prospective longitudinal data have been scarce until this publication. As part of a longitudinal child development study that recruited a representative sample from the Quebec birth registry, these investigators provided annual self-administered questionnaires to mothers on children's sleep terrors starting at age 1.5 years and somnambulism starting at age 2.5 years; assessments ended at age 13. At age 10, mothers were asked about parental sleepwalking.

At baseline, 1940 children were enrolled; attrition led to 1010 cases by age 13. Prevalence of sleep terrors decreased from 34% at age 1.5 to 5% at age 13. Prevalence of sleepwalking increased from 4% at age 2.5 to 13% at age 13. About 33% of children with sleep terrors also developed somnambulism. Prevalence of sleepwalking increased with the number of affected parents (22% with none, 47% with one, and 62% with both).

Depressed Pregnant Mothers — and the Antidepressants They Take — Leave Enduring Marks on Offspring

Joel Yager, MD reviewing Nemoda Z et al. *Transl Psychiatr* 2015 Apr 7. Brandlistuen RE et al. *Int J Epidemiol* 2015 Apr 14.

In one study, untreated maternal depression altered children's DNA methylation patterns of genes affecting immune function and stress reactivity; in another study, prenatal exposure to antidepressants increased anxiety in 3-year-olds.

Both maternal depression and prenatal antidepressant treatment can affect developing children, but specific mechanisms linking these antecedents to outcomes are not fully understood. Two recent studies add to our knowledge.

Nemoda and colleagues focused on epigenetic phenomena. In 15 currently depressed and 14 formerly depressed pregnant women and 15 matched nonpsychiatric controls, they examined genome-wide DNA methylation patterns in T lymphocytes from mothers' antepartum blood and neonatal cord blood. All participants were nonmedicated. Whereas methylation patterns in maternal blood were similar across groups, they differed by group in cord blood; neonatal cord blood from mothers with current or past depression showed enriched methylation patterns involving genes that regulate immune function and stress reactivity. Postmortem hippocampal tissue from men with depressed versus nondepressed mothers was also examined. DNA methylation patterns in men with depressed mothers were similar to the cord blood findings, including enrichment of genes regulating immune functions; 33 genes overlapped in the two samples.

To examine effects of prenatal antidepressant exposure on behavioral outcomes, Brandlistuen and colleagues analyzed data on a subset of siblings from a population-based Norwegian study who were discordant for prenatal antidepressant exposure. Analyses adjusted for maternal lifetime depression and prenatal depression, anxiety, smoking, alcohol use, and other medication use. In 121 siblings at age 36 months, prenatal exposure was associated with significantly more anxiety, but not greater emotional reactivity, somatic complaints, sleep problems, attention problems, or aggression.

CRISPR-Cas9 Is a Powerful New Gene-Editing Technique

Anthony L. Komaroff, MD reviewing Ran FA et al. *Nature* 2015 Apr 9. Liang P et al. *Protein Cell* 2015 May. Baltimore D et al. *Science* 2015 Apr.

But scientists raise concerns about potential adverse effects and other ethical issues.

A relatively new gene editing technology called CRISPR-Cas9 already is affecting basic biological research profoundly and holds promise for treating human disease. In three recent papers, researchers report advances and grounds for concern.

A team from MIT and Harvard reported a modification of the CRISPR technique that could escalate its potential for editing genes in living animals. The team targeted the *pcsk9* gene, which is important in cholesterol metabolism and is inhibited by a new class of drugs (*NEJM JW Gen Med* May 1 2015 and *N Engl J Med* 2015 Mar 15; [e-pub]). About 40% of hepatocytes in living mice contained the edited gene, leading to prompt and marked reductions in total cholesterol. The gene editing apparently did not induce any adverse effects.

One theoretical use of CRISPR technology would be to edit defective genes in human zygotes and then implant those zygotes following in vitro fertilization procedures. A team from China tested whether the technique could be used to edit genes in human zygotes. To avoid ethical issues, they used zygotes in which two sperm had entered a single egg — because such zygotes cannot produce viable fetuses. They found that, in such zygotes, the CRISPR technology was very inefficient and also produced “off-target,” potentially adverse effects.

In a perspectives article, a group of distinguished biologists strongly urges that CRISPR technology not be used to attempt germline modification for clinical application in humans; they argue that biologists first need to know much more about possible “off-target” effects (and “on-target” effects with unintended consequences). They urge the formation of multidisciplinary groups of biologists, clinicians, social scientists, legal scholars, ethicists, and representatives of government to chart a course.

Antidepressant Use During Early Pregnancy and Risk for Birth Defects

Paul S. Mueller, MD, MPH, FACP reviewing Furu K et al. BMJ 2015 Apr 17.

Selective serotonin reuptake inhibitors and venlafaxine do not appear to be major teratogens. Previous studies have yielded conflicting results on the teratogenic effects of selective serotonin reuptake inhibitors (SSRIs) and the serotonin-norepinephrine reuptake inhibitor venlafaxine. In this multinational, population-based cohort study, investigators assessed maternal SSRI or venlafaxine use and risk for birth defects in 2.3 million infants born between 1996 and 2010 in Nordic countries. To adjust for potential confounding from family-related factors, sibling-controlled analyses were performed using a cohort of sibling pairs (2288 infants) who were discordant for both maternal SSRI or venlafaxine use and birth defects.

Among 37,000 infants with first-trimester exposure to SSRIs, 3.7% had major birth defects, and 1.5% had cardiac-related birth defects; whereas, among 2.27 million unexposed infants, 3.2% had major birth defects, and 1.2% had cardiac-related birth defects (adjusted odds ratios, 1.13 and 1.15, respectively). No significant association was found between venlafaxine use and birth defects. In sibling-controlled analyses, SSRI or venlafaxine use was not associated with higher prevalence of major birth defects or cardiac-related birth defects.

Metabolic Monitoring for Patients on Antipsychotic Medications

Psychiatric Times

Tony Cohn, MD

CME | December 20, 2013 | Metabolic Disorders, CME, Psychopharmacology, Psychotic Affective Disorders

By Tony Cohn, MD

In this CME article, the focus is on the significance of metabolic changes that develop during antipsychotic treatment, as well as on strategies to incorporate metabolic monitoring into clinical practice.

Premiere Date: December 20, 2013

Expiration Date: December 20, 2014 [Expired]

This activity offers CE credits for:

1. Physicians (CME)
2. Other

All other clinicians will either receive a CME Attendance Certificate or may choose any of the types of CE credit being offered.

Activity Goal

This article provides the rationale for monitoring parameters in patients who are being treated with antipsychotics.

Learning Objectives

At the end of this CE activity, participants should be able to:

1. Recognize the importance of metabolic monitoring.
2. Describe what the goals and challenges are of monitoring patients.
3. Describe who, when, and how to monitor.

Target Audience

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

Credit Information

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Tony Cohn, MD, reports that he is on the Speaker's Bureau for Pfizer Canada, and he is a consultant for HInext.

Peter Buckley, MD (peer/content reviewer), has no disclosures to report.

Applicable Psychiatric Times staff have no disclosures to report.

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The focus on metabolic conditions in serious mental illness dates from the switch to atypical antipsychotics starting in the late 1990s. Metabolic conditions may include type 2 diabetes mellitus, hyperlipidemia, weight gain, obesity, metabolic syndrome, and associated coronary heart disease. The rationale for monitoring metabolic parameters during the course of antipsychotic treatment is clear.

- Reduced life expectancy in serious mental illness because of metabolic comorbidity (obesity, type 2 diabetes mellitus, dyslipidemia, coronary heart disease)
- Impact on quality of life
- Contemporary antipsychotics have prominent metabolic adverse effects
- Increased susceptibility to metabolic disorder because of genetic (thrifty phenotype) and lifestyle (diet, physical inactivity, cigarette smoking) factors
- Individuals with serious mental illness often receive suboptimal primary and preventive health care

Metabolic adverse effects of antipsychotics have been the subject of litigation and the focus of much media attention. There is considerable public awareness that compels clinicians to pay attention to these issues when prescribing antipsychotics. Metabolic adverse effects have clearly overtaken neurological adverse effects as a major concern in treating psychosis. As clinicians, we need to incorporate metabolic monitoring into clinical practice and to understand the significance of metabolic changes that develop during antipsychotic treatment.

The challenges

While there has been agreement about the importance of metabolic monitoring for close to a decade, practice audits consistently show low rates of adherence to monitoring guidelines. In a recent international review of guideline-concordant monitoring for metabolic risk in patients treated with antipsychotics, adherence was "concerningly low" in routine clinical practice. Monitoring rates remained low even after the widespread introduction of local and national guidelines starting from 2004. In a comparison of pre- and post-guideline practices, only glucose monitoring showed a statistically significant incremental increase.

The reasons for low monitoring tend to be system-related. For example, is monitoring the responsibility of the psychiatrist or of a primary care physician? Mental health practitioners may not be up-to-date or comfortable assessing and interpreting metabolic parameters. Patients with serious mental illness may not have access to primary care and may not follow through with laboratory testing or medical appointments. What action should be taken when laboratory test results are abnormal? Clinicians are busy and, thus, often systematic metabolic monitoring is not completed or sustained during the course of treatment.

One of the most concerning consequences of this is that clinical decisions are based on limited data. For example, a patient is found to have diabetes well into the course of antipsychotic treatment. The antipsychotic is switched and the patient decompensates. Without systematic monitoring, it is unclear how long the patient has had diabetes and what the relationship was to the prescribed antipsychotic. Or, clozapine is not prescribed for a diabetic patient with refractory psychosis because the clinician is convinced that there will be further weight gain and worsening of diabetes. With careful metabolic monitoring, this may well not be the case, and if there is worsening glucose control, diabetes medication can be easily adjusted.

Goals and guidelines

The goals of metabolic monitoring are:

- Early identification of treatable metabolic conditions (diabetes, dyslipidemia, and hypertension)
- Identification of individuals at high risk for metabolic disorder (metabolic syndrome, prediabetes, severe obesity) for prevention and health promotion initiatives
- Evaluation of the association between prescribed antipsychotic medication and the development of metabolic disorder by collecting systematic clinical data
- Evaluation of the outcome of metabolic interventions (antipsychotic switching, pharmacotherapy, and psychotherapy)

In North America, the key metabolic monitoring guideline is the American Diabetes Association (ADA)/American Psychiatric Association (APA) consensus document that quickly became the standard reference soon after its publication in 2004. The guideline specifies baseline and interval monitoring of glucose and lipid parameters and a review of the patient's medical history and physical measurements, including weight, waist circumference, and blood pressure. In 2010, the ADA added hemoglobin A1c as a diagnostic test for diabetes, which facilitates diabetes screening because overnight fasting is not required for this test. Obtaining fasting blood samples can be challenging when working with patients who have a serious mental illness. Moreover, monitoring lipid parameters annually is preferable to every 5 years, as suggested in the original guidelines. These modifications are included in Table 1.

Other international guidelines include the position paper of the European Psychiatric Association, supported by the European Association for the Study of Diabetes and the European Society of Cardiology. Similar guidelines have also been developed in Australia, Canada, France, and Sweden. There is considerable consensus across the monitoring guidelines. Special guidelines have also been developed for monitoring metabolic changes in children and adolescents treated with antipsychotics.

Baseline monitoring is particularly important when an antipsychotic is first prescribed and when patients are switched to an antipsychotic with high metabolic liability, such as clozapine or olanzapine. This establishes a baseline from which to evaluate subsequent changes in metabolic parameters. Monitoring 3 months after the initial baseline is valuable in assessing early metabolic change.

Young, antipsychotic-naïve patients are particularly susceptible to rapid weight gain. Change in body weight and an increase in triglyceride levels are the usual early metabolic changes; fasting glucose and hemoglobin A1c levels generally remain low initially because of compensatory hyperinsulinemia. Rising insulin levels can be a useful marker of early metabolic change, but insulin levels are not measured routinely because assays are not well standardized and because costs can be prohibitive. Occasionally, acute onset of diabetes can be picked up at the 3-month point; this is a clear indication for discontinuing or switching the antipsychotic.

Antipsychotics are prescribed long-term. Therefore, establishing a routine of annual metabolic monitoring is important so that metabolic changes can be tracked and dealt with as they arise throughout the course of treatment.

Practical considerations

There is debate about who should be responsible for metabolic monitoring. Because mental health practitioners are often the primary health care contacts for patients with serious mental illness, it may be that the responsibility for metabolic monitoring, but not necessarily treatment of metabolic disturbance, rests with mental health practitioners. At the same time, experience has shown that systems and structures need to be established to support routine monitoring. In practice, basic psychiatric care may need to be augmented by physical health clinics and/or metabolic clinics as well as by regular audits to ensure adherence with guidelines and appropriate follow-through.

At the same time, the responsibility for monitoring oversight remains in the realm of mental health, and a basic "metabolic knowledge base" needs to be developed. In practical terms, mental health practitioners should know:

In primary and general medical practice, the relevance and importance of metabolic syndrome as a construct and as a risk marker are often debated. Guidelines for the management of hyperlipidemia are grounded on the Framingham assessment, which is based on total and low-density lipoprotein cholesterol levels. Moreover, 4 of the 5 metabolic syndrome criteria—

metabolic dyslipidemia (raised triglyceride and low high-density lipoprotein cholesterol levels), abdominal adiposity (increased waist circumference), and dysglycemia (increased glucose levels)—are markers of antipsychotic metabolic effects. Not surprisingly, rates of metabolic syndrome are consistently elevated in adult samples of patients with serious mental illness, and fasting insulin levels (equivalent to metabolic syndrome) are elevated in younger patients with early psychosis. Therefore, it can be argued that metabolic syndrome has added relevance as a risk marker for patients treated with antipsychotics, an issue often not recognized by primary care providers.

In terms of equipment, practitioners should have a digital scale, blood pressure cuff, and tape measure easily accessible in the office. Office scales only measure up to 300 or 350 lb; clinics or hospitals should ensure access to a more advanced scale for patients who weigh more. Practitioners may find it useful to designate 1 month of every 6 or 12 months to focus on metabolic monitoring and to ensure that every patient in the caseload is monitored.

Whom to monitor

It helps to define the population. Many will define this as any patient who is taking regularly prescribed antipsychotics. Some would also include those receiving mood stabilizers or antidepressants because these drugs are associated with weight gain. If there is a need to focus on a smaller target, one might choose the highest-risk groups—patients with early psychosis, those receiving clozapine who are already having routine blood work, forensic patients who are confined for long periods in hospitals or jails, or high-risk ethnic groups (Hispanic, South Asian, Aboriginal, or black).

When to monitor

It is best to start immediately and monitor patients who have not been monitored recently. Baseline monitoring is important when an antipsychotic is first prescribed for a new patient; it will be extremely valuable if problems later emerge. When a patient's medication is switched, particularly to a high-liability agent, getting another baseline is again valuable. Setting up reminders or a system for annual monitoring is important, as is checking 3 months after the initial baseline. More frequent monitoring is usually unnecessary and redundant unless there is a specific clinical focus or concern.

How to monitor

This might present the biggest challenge. There is a need for data collection, data entry, and documentation. In our center, we have developed an electronic tool that organizes these tasks, integrates with the laboratory system, analyzes the data, and flags areas of concern. Computer systems are well suited to this task and allow for auditing and reports. Paper-based tracking records are also used. The task of data collection and data entry can be delegated, but the prescribing clinician should maintain responsibility for ensuring that the monitoring is completed and for reviewing results.

Follow through

This involves collaboration with primary care providers and other clinicians. Referrals must be made when there is a new diagnosis of diabetes, hypertension, or significant dyslipidemia or when diabetes is poorly controlled. Patients will need support to follow through with appointments and treatment. When uncertain, clinicians may find it helpful to fax results to the primary care physician or to consult a colleague. When high-risk patients are identified (prediabetes, metabolic syndrome, severe obesity), referral to a dietitian or metabolic clinic is indicated.

Antidepressant Therapy in Older Adults: A Network Meta-Analysis

Allan S. Brett, MD, Peter Roy-Byrne, MD reviewing Thorlund K et al. *J Am Geriatr Soc* 2015 May.

Sertraline seemed to strike the best balance between efficacy and tolerability.

In a recent meta-analysis of randomized, placebo-controlled trials, researchers found antidepressant drugs — analyzed collectively — to be only minimally better than placebo in older patients (age, ≥ 60) with relatively recent-onset major depressive disorders (*NEJM JW Gen Med* Jul 15 2013 and *Am J Psychiatry* 2013; 170:651).

Now, another research team has performed a network meta-analysis of efficacy and safety of individual selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors (SSRIs and SNRIs) for patients with major depression in this age group. Network meta-analysis makes indirect comparisons between drugs that have not been compared directly in head-to-head trials. The analysis included 15 randomized trials involving seven selective SSRIs and SNRIs. Trials were short (6–12 weeks) and of varying size (27–728 participants); mean age ranged from 67 to 80.

Statistically significant partial responses were noted for sertraline, paroxetine, and duloxetine (but not for citalopram, escitalopram, venlafaxine, or fluoxetine). Dizziness was the only adverse effect that could be analyzed across studies: Duloxetine and venlafaxine were most likely to cause dizziness, and sertraline was least likely.

Maternal Stroking Affects Infant Glucocorticoid Receptor Methylation

Barbara Geller, MD reviewing Murgatroyd C et al. *Transl Psychiatry* 2015 May 5.

An association was found only in the context of low prenatal depression followed by postpartum depression.

In rat studies, pups that have been licked and groomed have lower methylation of the glucocorticoid receptor gene (GR) and fewer anxiety behaviors than pups without these maternal actions (*NEJM JW Psychiatry* Sep 23 2004 and *Nat Neurosci* 2004; 7:847 and 791). To translate these findings to humans, investigators studied 181 women and their infants.

Mothers' depression was rated at 20 and 32 weeks' gestation. At 5 and 9 weeks postpartum, ratings of maternal depression, infant stroking, and infant GR methylation were obtained. Selection of GR locus was based on previous findings in the literature. Analyses controlled for multiple substance use and obstetric variables.

Prenatal and postnatal depressions were highly correlated to each other and significantly associated with higher methylation. Sixteen mothers experienced low prenatal depression and high postnatal depression; in their infants, low levels of maternal stroking at age 5 weeks correlated with high GR methylation.

FREE WORKSHOP
On
Psychiatric Illnesses
at Karachi Psychiatric Hospital

Date 30-05-2015



Karachi Psychiatric Hospital held the monthly workshop.

Topic: Schizophrenia

World No Tobacco Day

Dated: 29-05-2015



سگریٹ مردے پیدا کرتی ہے

On the occasion of World No Tobacco Day
M.D. Karachi Psychiatric Hospital
Dr. Syed Mubin Akhtar held a
Press Conferences and Demonstration