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(Drug Addiction is Curable and Manageable)

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At

Karachi Psychiatric Hospital

Table of Contents

1. Short-Term Use of Oral Corticosteroids Tied to Sepsis, VTE, and Fracture.	292
2. SuperAgers: Bigger Brains or Less Loss?	293
3. Late-Life Mentally Stimulating Activities and Incident Mild Cognitive Impairment.	294
4. Sleep Medicine Group: Adolescents' School Day Should Not Start Before 8:30 A.M.	295
5. Violence in Bipolar Disorder.	295
6. Diet Drinks Linked to Increased Risk for Stroke and Dementia.	301
7. Targeting the Microbiota-Gut-Brain Axis: Probiotics Have Anxiolytic and Antidepressant-like Effects and Reverse the Impact of Chronic Stress in Mice.	303
8. Outcomes of Integrated Behavioral Health with Primary Care.	304
9. Celiac Disease and Anorexia Nervosa: Are They Connected?	305
10. A Novel Neurofeedback Intervention for Depression.	306
11. Violence Toward Self Is Linked to Violence Toward Others.	307
12. Do Antidepressants Contribute to the Risk for Dementia?	308
13. Adult Outcomes of First Suicide Attempts in Children Versus in Adolescents.	309
14. Should We Treat Patients with Subclinical Hypothyroidism?	310
15. Psychogenic Non-Epileptic Seizures: Clinical Issues for Psychiatrists.	311
16. Update on Medical Catatonia: Highlight on Delirium.	321
17. Doctors and Marriage: Should You Have a Prenuptial?	327
18. Pharmacotherapy for alcohol use disorder.	332

Short-Term Use of Oral Corticosteroids Tied to Sepsis, VTE, and Fracture

By Amy Orciari Herman

Edited by André Sofair, MD, MPH, and William E. Chavey, MD, MS

Short-term use of oral corticosteroids is associated with increased risks for sepsis, venous thromboembolism (VTE), and fracture, according to an observational study in *The BMJ*.

Using a large U.S. health claims database, researchers studied 1.5 million adults under age 65, of whom 21% received prescriptions for short-term (<30 days) oral corticosteroids over a 3-year period. Overall, corticosteroid users, compared with nonusers, had a higher incidence of sepsis (1.8 vs. 1.0 events per 1000 person-years), VTE (4.6 vs. 2.4 per 1000), and fracture (21.4 vs. 14.3 per 1000).

A separate analysis in which corticosteroid users served as their own controls strengthened the findings: the incidence of sepsis, VTE, and fracture each increased during the first 30 days of corticosteroid use, relative to the period before corticosteroid use.

The researchers note, "Our findings are particularly of concern given the large number of patients exposed to short term oral corticosteroids in the general adult population."

SuperAgers: Bigger Brains or Less Loss?

Jaime Toro, MD reviewing Cook AH et al. JAMA 2017 Apr 4

Adults older than 80 with above-average memory had slower brain volume loss than elders with average memory.

So-called SuperAgers are defined as people over age 80 who have unusually high performance on tests of episodic memory. These individuals also have higher cortical thickness on structural magnetic resonance imaging (MRI) than their healthy age-matched peers and show no atrophy compared to 50- to 65-year-old healthy individuals. Whether SuperAgers simply start with a thicker cortex or have less volume loss with age is unclear.

To examine brain volume change over 18 months, researchers recruited individuals 80 years and older with normal daily functioning. The 24 SuperAgers (75% women; mean age, 83.3 years) scored at or above the norm for adults aged 50 to 65 years on tests of episodic memory and at age norm or above on other cognitive domains. Both SuperAgers and 12 cognitively average elders (42% women; mean age, 83.4) showed significant loss of whole brain cortical volume (SuperAgers, 1.06% annual change; cognitive average elders, 2.24%). The annual loss was significantly greater (by 1.18%) in cognitively average elders than in SuperAgers, both before and after adjustment for sex, handedness, and education.

COMMENT

This study shows that differences in cognitive performance among healthy older adults identified as SuperAgers is related at least in part to differences in rate of brain volume loss. Whether SuperAgers also start with thicker cortex remains unclear. Unimpaired cognition is important in successful aging. Future studies must evaluate associations between brain structure and cognition in older individuals and across the adult lifespan.

Late-Life Mentally Stimulating Activities and Incident Mild Cognitive Impairment

Jennifer Rose V. Molano, MD reviewing Krell-Roesch J et al. JAMA Neurol 2017 Mar 1

Mentally stimulating activities may decrease the risk for mild cognitive impairment in late life.

To evaluate the effect of late-life mentally stimulating activities on the incidence of mild cognitive impairment (MCI), researchers conducted a longitudinal, population-based study. The 1929 participants (median age, 77) completed a questionnaire about mentally stimulating activities within 1 year of enrollment. Neuropsychological testing was performed at baseline and every 15 months. Cognitive status was determined by an expert consensus panel. Apolipoprotein E ϵ 4 status was also obtained.

Of the participants, 512 were apolipoprotein E ϵ 4 carriers, and 456 developed MCI during about 4 years of follow-up. After adjustment for age, sex, and education, mentally stimulating activities performed at least 1 to 2 times a week were associated with a decrease in MCI risk of 22% for playing games, 28% for craft activities, 30% for computer uses, and 23% for social activities. Reading books did not significantly affect MCI risk. Craft activities, computer use, and social activities were associated with an approximate 25% risk reduction for amnesic MCI. Only computer use was associated with a decreased risk for nonamnesic MCI. The lowest MCI risk was seen in apolipoprotein E ϵ 4 noncarriers who performed mentally stimulating exercises (except for craft activities), and the highest MCI risk was seen in apolipoprotein E ϵ 4 carriers who did not perform mentally stimulating activities.

COMMENT

Consistent engagement in mentally stimulating activities may reduce the risk for MCI in late life. Effects may be modified by apolipoprotein E ϵ 4 status. Although these results are promising, other lifestyle factors such as physical exercise and diet may affect cognitive status and should be considered in the overall assessment of patients. Controlling other risk factors for cognitive decline, including hypertension, diabetes, and obesity, also remain important.

Sleep Medicine Group: Adolescents' School Day Should Not Start Before 8:30 A.M.

By Amy Orciari Herman

Edited by David G. Fairchild, MD, MPH

The American Academy of Sleep Medicine, in a new position statement, says the school day for middle and high school students should begin at 8:30 a.m. or later.

Earlier school start times work against adolescents' natural circadian rhythms, the group says, which cuts their sleep short and leads to chronic sleep deprivation. Such sleep loss, in turn, has been associated with poor academic performance, obesity, metabolic dysfunction, and depressive symptoms, among other outcomes.

"Starting school at 8:30 a.m. or later gives teens a better opportunity to get the sufficient sleep they need to learn and function at their highest level," the statement's lead author said in a press release. The AASM recommends that teens sleep 8–10 hours per night.

Violence in Bipolar Disorder

By Allison M. R. Lee, MD and Colleagues

TABLE

Ten historical items from the Historical, Clinical, and Risk Management (HCR-20) violence assessment scheme²⁸

- Violence
- Other antisocial behavior
- Relationships
- Employment
- Substance use
- Major mental disorder
- Personality disorder
- Traumatic experiences
- Violent attitudes
- Treatment or supervision response

The relationship between mental illness and violence is controversial. On the one hand, there is considerable unfounded stigma and discrimination toward the mentally ill based on the popular notion that psychiatric patients are dangerous people. On the other hand, there is a legitimate need for psychiatrists to identify and manage what risk of violence does exist in their patients. Research that examines how and why violence occurs in the mentally ill is necessary for psychiatrists to determine as accurately as possible which patients are prone to violence and to manage their care accordingly.

Traumatic experiences in childhood have been linked to the potential for violence in adulthood as well as to vulnerability to psychiatric disorders. Bipolar disorder has been linked to traumatic childhood experience and to the potential for violence.

In this review, we explain the association between bipolar disorder, trauma, and violence, and we suggest ways of assessing violence potential in bipolar patients.

Childhood trauma in bipolar disorder

DSM-5 defines trauma as exposure to an event that involves “actual or threatened death, serious injury, or sexual violence.” The traumatic event can be experienced firsthand or by learning that the event occurred in a close family member or friend. Moreover, the traumatic event is experienced repeatedly or there is extreme exposure to the details of the event.

A history of childhood traumatic experience has been associated with increased vulnerability to multiple mental disorders, including mood disorders and personality disorders. Etain and colleagues⁶ found that a history of 2 or more types of trauma is associated with a 3-fold increase in the risk of bipolar disorder. Prognosis and course of bipolar disorder are worse when there is a history of trauma. Trauma history is associated with earlier onset of bipolar disorder; faster cycling; increased rates of suicide; and more comorbidity, including anxiety disorders, personality disorders, and substance use disorders.

Etain and colleagues have shown that in patients with bipolar disorder, more than 50% report childhood trauma, with a high incidence of emotional abuse; 63% of the patients had experienced 2 or more forms of trauma as well as more severe forms. Conus and colleagues found that about 80% of patients with bipolar disorder had experienced at least 1 stressful life event. Among them, 16% had been physically abused, 15% had been sexually abused, 40% had experienced parental separation, and 20% had problems with a partner.

There are several pathways by which childhood trauma could lead to the development of bipolar disorder. Any one or a combination of these pathways could be operational in the development of bipolar disorder in individuals who have experienced childhood trauma. Thus, either the

trauma itself or the factors that lead to trauma—or both—could affect the development and course of bipolar disorder.

- Affective disturbances in relationships between parents and their children directly predispose the children to affective disturbances in adulthood
- Children in whom bipolar disorder later develops are prone to more behavioral disturbances in childhood (a prodrome, or early onset, of bipolar disorder), which could disrupt relationships with parents and lead to dysfunctional parenting
- Children of affectively ill parents could be affected by genetic transmission of affective illness predisposition as well as by parental psychopathology, which increases the likelihood of childhood trauma

The link between trauma and violence in bipolar disorder

Childhood trauma history has been found to correlate with increased aggression in adults with and without affective disorders. In addition, there is an overlap between the neurochemical changes found in adults with histories of traumatic stress and those found in adults with increased impulsive aggression—in particular, increased functioning of both the catecholamine system and the hypothalamic-pituitary-adrenal axis.

The prevalence of childhood trauma in persons with bipolar disorder combined with the risks that arise from the symptoms of the disorder itself renders bipolar patients at increased risk for violent behavior. Because childhood trauma has been associated with earlier onset and a greater number of episodes, there is more cumulative time when aggressive behavior is most likely to manifest. In addition, a history of trauma is associated with an increase in rates of substance abuse, which itself is associated with significant violence risk. Aggressiveness is often shown in different clinical settings, including bipolar, borderline, and antisocial personality disorders. Comorbidity with borderline personality disorder is associated with a higher risk of aggression in bipolar disorder during periods of euthymia.

Violence and aggression

Persons with bipolar disorder are at significantly increased risk for violence, with some history of violent behavior ranging from 9.4% to just under 50%, often in the presence of comorbid diagnoses. Bipolar patients are prone to agitation that can result in impulsive aggression during manic and mixed episodes. However, depressed states can involve intense dysphoria with agitation and irritability, which can also increase the risk of violent behavior. Bipolar patients may have chronic impulsivity during euthymia, predisposing them to aggression. This is especially true with comorbid features of borderline personality disorder. In fact, particularly

high levels of impulsivity and aggression in a bipolar patient could be a strong indicator of comorbidity with borderline personality disorder.

Impulsive aggression (as opposed to premeditated aggression) is most commonly associated with bipolar and other affective disorders. In animal models, premeditated aggression corresponds to predatory behavior, while impulsive aggression is a response to perceived threat (the fight in fight-or-flight). As either a state or trait, increased impulsive aggression is driven by an increase in the strength of aggressive impulses or a decrease in the ability to control these impulses. Neurochemically, impulsive aggression has been associated with low serotonin levels, high catecholamine levels, and a predominance of glutamatergic activity relative to γ -amino-butyric acid (GABA)ergic activity.

Assessing violence risk

In many ways, the assessment of violence risk in patients with bipolar disorder is similar to risk assessment in any patient. Certain data from the patient's history and mental status examination are universally important:

- A history of violent acts, especially recent ones and especially if there were any legal consequences.
- The extent of alcohol and drug use, because there is a strong association between substance abuse and risk of violence.
- Trauma history has a unique relationship with bipolar disorder, and it should be assessed in all patients to determine the risk of violence. Trauma is associated with increased aggression in adults in general, regardless of whether an affective disorder is present.
- Other important historical data include demographic information (young men of low socioeconomic status who have few social supports are the most likely to be violent) and access to weapons.
- In the mental status assessment, it is important to note psychomotor agitation as well as the nature, frequency, and severity of violent ideation.
- Use of an actuarial instrument, such as the Historical, Clinical, and Risk Management-20 (HCR-20) violence assessment scheme, can help integrate systematic inquiry about evidence-based risk factors into assessment of the clinical scenario. Although such instruments are often developed for use in forensic populations, they can be integrated into the assessment of other populations; for example, the 10 historical items of the HCR can be used as a structured checklist in conjunction with a clinical assessment (**Table**).

In assessing patients with bipolar disorder, pay special attention to violent behavior that may have occurred when the person was manic. Also consider violence during euthymic periods, especially in patients who are substance abusers or who have Axis II comorbidity. If at all possible, obtain collateral information about the history of violence. Patients may minimize previous violent actions or not remember them, especially if they were in the midst of a manic episode.

Bipolar patients are most prone to violence during manic or mixed states—when maximum behavioral dyscontrol is combined with unrealistic beliefs. Patients with dysphoric mania and mixed states may be at especially high risk; the assessment for concurrent depression in a manic patient should therefore be a priority.

Symptoms of bipolar disorder often overlap with those of borderline personality disorder. Comorbid borderline personality disorder, which is often associated with trauma history, has been shown to predict violence potential in bipolar patients, especially during periods of euthymia. Impulsivity is a prominent feature of bipolar disorder. Information about previous impulsive acts, especially acts of impulsive aggression, can give the clinician an idea of a person's likelihood to commit violence on impulse. Often, patients with bipolar disorder will use alcohol and other drugs to self-medicate mood episodes or as part of the pleasure-seeking behavior of a manic episode.

Prevention and management of violence in bipolar patients

The bipolar diagnosis introduces some unique aspects to violence prevention and management, although the general principles are similar to those for patients with other disorders. There are 7 areas that are particularly important in the prevention and management of violence in bipolar patients.

A positive treatment alliance. This can be a challenge in bipolar patients who may have low motivation for treatment, especially if they have poor insight or if they enjoy their manic symptoms. In addition, a history of childhood abuse can lead to diminished capacity for trust and collaboration with the clinician. To improve the alliance with a reluctant bipolar patient, identify his or her particular barriers to acceptance of treatment and work to diminish them. It may be helpful to normalize the enjoyment of mania and to empathize with the patient's resistance to treatment as an understandable desire to be healthy and independent.

Frame treatment that addresses aggressive behavior in a way that respects the patient's desire for control; for example, convey that the medication will help the patient control himself rather than saying that the medication will control the patient. A collaborative approach maximizes the patient-physician alliance.

Treat the mood episode. Because the risk of violent behavior increases during an episode, the sooner mood symptoms can be ameliorated the lower the risk. In addition to the agitation and hyperactivity of mania (or sometimes depression), psychotic symptoms are important targets of violence prevention. Symptoms such as paranoid delusions or command auditory hallucinations can contribute to violent behavior, with a greater number of psychotic-like experiences associated with a higher risk of violence. Mixed states may be especially high-risk and may respond better to valproate than to lithium.

Involve significant others. Those close to a person with bipolar disorder can be both potential victims of aggressive behavior and potential sources of help in symptom monitoring, especially for patients with poor insight. Determine with the patient and family what the early warning signs of a mood episode are for that person so that intervention can be instituted early, before behavior becomes unmanageable. Educating friends and family can prevent violence by helping them avoid behavior that could worsen the patient's aggression; help them understand the need to leave a situation that may become volatile and when urgent intervention is needed (eg, calling 911).

Treat emotional lability and impulsivity. Bipolar patients may be impulsive even during euthymia, especially if there is comorbid borderline personality disorder. Consider referring the patient for dialectical behavioral therapy if borderline features dominate the clinical picture or if there is a significant history of impulsive risk taking or self-harm during euthymia.

Treat substance abuse. Substance use disorders are highly comorbid with bipolar disorder and are a major risk factor for violence. Aggressively assess and treat such disorders, and refer the patient to specialized outpatient programs or restrictive residential programs, if needed.

Teach coping skills. Use assertiveness training, social skills training, anger management training, and stress management training as needed to help the person express his needs, manage potentially frustrating interactions, avoid stress, and handle any anger that arises.

Manage emergencies. If a bipolar patient is an acute danger to others, steps must be taken to incapacitate him. These include involuntary hospitalization and medication. Bipolar patients are most often involuntarily hospitalized during manic episodes. An aggressive pharmacological approach should be taken to address the manic symptoms so as to quickly diminish the risk of aggressive behavior.

Aside from treating the manic episode, other measures may be used if needed to quickly control aggressive behavior. These include sedating medication (eg, benzodiazepines, antipsychotics), seclusion, and restraint. It is important to provide an environment that minimizes overstimulation and includes clear interpersonal communication and limit-setting.

Summary

Bipolar disorder is associated with a high prevalence of childhood trauma as well as with the possibility of aggressive and potentially violent behavior. It is important for clinicians to assess a patient's potential for violence as accurately as possible to minimize risk. Taking clinical and historical information into account, such as mood symptoms and history of violence, substance abuse, childhood trauma, and impulsivity, can help clinicians make an accurate assessment.

Handling emergencies and treating mood episodes pharmacologically are first steps in managing risk; this should be followed up with treating substance abuse and trait impulsivity and with involving significant others and teaching coping skills. Recognizing the impact of early trauma on a patient can help improve the therapeutic alliance and lead to better outcomes.

Diet Drinks Linked to Increased Risk for Stroke and Dementia

Study confirms potential concerns about consuming two or more diet drinks a day.

Too many diet drinks may take a toll on the brain, based on a recent study that linked two or more diet drinks a day to increased risk for stroke and dementia.

Published in the American Heart Association journal *Stroke*, this study looked at the long-term impact of sugar and artificially sweetened beverages on the brain.

While we know that too many sugary drinks have a negative impact on heart health, studies suggest they may increase risk for stroke and dementia. A few studies have also linked artificially sweetened beverages like diet soda to increased risk for stroke. However, evidence has been conflicting and the issue remains highly debated.

To help settle the debate, researchers analyzed data from the Framingham Heart Study, which included more than 4,300 adults in Framingham, Massachusetts.

Between 1991 and 2001, participants completed questionnaires on their diet and beverage consumption. Researchers then followed participants for ten more years, tracking any cases of stroke and dementia.

Since dementia is rare in younger adults, the study included two groups of adults. One group consisted of 1,484 adults over 60 years old, who were followed for dementia. The second group included 2,888 adults 45 years or older, who were followed for stroke.

Overall, there were 97 strokes and 81 cases of dementia observed during the follow-up period. After analysis, researchers found that diet beverages were associated with increased risk of stroke and dementia, while sugary beverages were not.

Compared to adults who consumed no diet beverages, those consuming 2 or more diet drinks a day had nearly three times greater risk of stroke and dementia.

However, it's important to consider some key limitations of the study. As authors explain, the study doesn't show that diet beverage consumption directly causes increased risk for stroke and dementia. It also included self-reported data, which is not 100% reliable, and doesn't rule out all potential factors that could impact this association. For example, researchers found that adults with diabetes were much more likely to consume diet beverages than those without diabetes. Therefore, it's possible that diabetes is more to blame for high rates of stroke and dementia than diet soda.

Researchers also note that when dietary questionnaires were completed during the '90s, only three artificial sweeteners were approved by the U.S. Food and Drug Administration—saccharin, acesulfame-K and aspartame. Since then, newer sweeteners have entered the market, which were not assessed in this study.

Still, findings are intriguing, as experts continue to explore the long-term effects of beverage consumption on health. In the meantime, experts stand by recommendations to limit consumption of both sugary and artificially sweetened beverages to promote good health.

Targeting the Microbiota-Gut-Brain Axis: Probiotics Have Anxiolytic and Antidepressant-like Effects and Reverse the Impact of Chronic Stress in Mice

Aurelijus Burokas and Colleagues

Abstract

Background

The realization that the microbiota-gut-brain axis plays a critical role in health and disease, including neuropsychiatric disorders, is rapidly advancing. Nurturing a beneficial gut microbiome with prebiotics, such as fructo-oligosaccharides (FOS) and galacto-oligosaccharides (GOS), is an appealing but underinvestigated microbiota manipulation. Here we tested whether chronic prebiotic treatment modifies behavior across domains relevant to anxiety, depression, cognition, stress response, and social behavior.

Methods

C57BL/6J male mice were administered FOS, GOS, or a combination of FOS+GOS for 3 weeks prior to testing. Plasma corticosterone, microbiota composition, and cecal short-chain fatty acids were measured. In addition, FOS+GOS- or water-treated mice were also exposed to chronic psychosocial stress, and behavior, immune, and microbiota parameters were assessed.

Results

Chronic prebiotic FOS+GOS treatment exhibited both antidepressant and anxiolytic effects. Moreover, the administration of GOS and the FOS+GOS combination reduced stress-induced corticosterone release. Prebiotics modified specific gene expression in the hippocampus and hypothalamus. Regarding short-chain fatty acid concentrations, prebiotic administration increased cecal acetate and propionate and reduced isobutyrate concentrations, changes that correlated significantly with the positive effects seen on behavior. Moreover, FOS+GOS reduced chronic stress-induced elevations in corticosterone and proinflammatory cytokine levels and depression-like and anxiety-like behavior in addition to normalizing the effects of stress on the microbiota.

Conclusions

Taken together, these data strongly suggest a beneficial role of prebiotic treatment for stress-related behaviors. These findings strengthen the evidence base supporting therapeutic targeting of the gut microbiota for brain-gut axis disorders, opening new avenues in the field of nutritional neuropsychopharmacology.

Outcomes of Integrated Behavioral Health with Primary Care.

Balasubramanian BA and Colleagues

Abstract

BACKGROUND:

Integrating behavioral health and primary care is beneficial to patients and health systems. However, for integration to be widely adopted, studies demonstrating its benefits in community practices are needed. The objective of this study was to evaluate effect of integrated care, adapted to local contexts, on depression severity and patients' experience of care.

METHODS:

This study used a convergent mixed-methods design, merging findings from a quasi-experimental study with patient interviews conducted as part of Advancing Care Together, a community demonstration project that created an innovation incubator for practices implementing evidence-based integration strategies. The study included 475 patients with a 9-item Patient Health Questionnaire (PHQ-9) score ≥ 10 at baseline, from 5 practices.

RESULTS:

Statistically significant reductions in mean PHQ-9 scores were observed in all practices, ranging from 2.72 to 6.46 points. Clinically, 50% of patients had a ≥ 5 -point reduction in PHQ-9 score and 32% had a $\geq 50\%$ reduction. This finding was corroborated by patient interviews that demonstrated positive experiences with behavioral health clinicians and acquiring new skills to cope with adverse situations at work and home.

CONCLUSIONS:

Integrating behavioral health and primary care, when adapted to fit into community practices, reduced depression severity and enhanced patients' experience of care. Integration is a

worthwhile investment; clinical leaders, policymakers, and payers should support integration in their communities.

Celiac Disease and Anorexia Nervosa: Are They Connected?

F. Bruder Stapleton, MD reviewing Marild K et al. *Pediatrics* 2017 Apr 3

A bidirectional association was observed in Swedish girls and women.

Anorexia nervosa (AN) has been linked to celiac disease (CD) in case reports. To test this possible association further, investigators conducted a retrospective, case-control, cohort study involving 17,959 women with CD (median age at diagnosis, 28 years; range, 6–52 years) and 89,379 age- and sex-matched, population-based controls identified in the Swedish national health registry.

From 1987 through 2009, during more than 1 million person-years of follow-up, patients with a biopsy-proven diagnosis of CD were more likely than controls to have later AN (27 vs. 18/100,000 person-years; hazard ratio, 1.46). Also, patients with AN were more likely than controls to have later CD (odds ratio, 2.18). In subgroups of patients with mucosal inflammation on bowel biopsy or abnormal CD serology but a normal CD biopsy, an association with AN before and after biopsy was also found. In a small group of men with AN, no association with CD was identified.

COMMENT

These results demonstrate that an association exists between AN and CD in Swedish girls and women. We should watch for the development of either diagnosis once one condition is identified. These data are noteworthy in light of the widespread public concern about dietary gluten. Editorialists raise the intriguing question of whether the voluntary avoidance of gluten for personal preference might lead to later AN.

A Novel Neurofeedback Intervention for Depression

Joel Yager, MD reviewing Young KD et al. Am J Psychiatry 2017 Apr 14

Real-time neurofeedback that used functional magnetic resonance imaging and increased amygdala blood-flow associated with positive memories reduced symptoms in moderately depressed patients.

In depressed patients, amygdala hemodynamic responses are attenuated with positive stimuli (e.g., happy memories) but are exaggerated with negative stimuli. Some studies have suggested clinical value for real-time functional magnetic resonance imaging neurofeedback (rtfMRI-nf) for anxiety, depression, chronic pain, and smoking cessation. In a randomized, double-blind study, investigators have now examined whether rtfMRI-nf aimed at increasing amygdala activity (i.e., blood-oxygen-level-dependent [BOLD] signals) in response to positive autobiographical memories might alleviate depressive symptoms in 36 unmedicated, moderately depressed adults.

About 75% of participants were chronically depressed; >50% had previously received antidepressants. The study arms were rtfMRI-nf focusing on the amygdala or, as a control, on the intraparietal sulcus (not thought to be involved in emotion regulation). The two rtfMRI-nf sessions, conducted 1 week apart and each lasting >1 hour, consisted of multiple trials and alternating rest periods, practice periods, and actual neurofeedback trials during which participants were asked to recall happy memories while up-regulating their BOLD signals (indicated visually by moving a red bar).

At follow-up (5–7 days after completion), the experimental group had significantly lower depression scores than the control group (response [$\geq 50\%$ reduction in depression-scale scores], 12 vs. 2; remission: 6 vs. 1; number needed to treat, 4) and increased capacity to recall positive memories. The experimental and control groups showed significantly increased activity in the amygdala and intraparietal sulcus, respectively, demonstrating the success of neurofeedback training. One patient in each group was unable to tolerate the procedures.

COMMENT

In this early trial, 33% of the experimental group achieved remission within 4 weeks. Further studies may reveal optimal training frequencies, intensities, and duration; how cost, acceptability, and effectiveness of rtfMRI-nf might compare with those of other interventions; and whether rtfMRI-nf improves more-severe depressions.

Violence Toward Self Is Linked to Violence Toward Others

Steven Dubovsky, MD reviewing Sahlin H et al. JAMA Psychiatry 2017 Apr 5

Results from a Swedish longitudinal registry study

Although deliberate self-harm (DSH) is often considered within the spectrum of suicidality, these researchers have examined another question in a longitudinal cohort study — how much people who engage in this behavior are likely to hurt other people. Swedish medical and legal registers of treatment were analyzed for any form of DSH and conviction for any crime. Participants were 1,850,525 people who were born between 1982 and 1998 and were at least 15 years old at the start of the study (mean follow-up, 8 years).

Fewer than 1% of episodes of DSH (N=55,185) were high risk (suffocation, strangulation); almost 95% involved nonlethal cutting and poisoning, and <5% involved medium risk-methods (drowning or gassing). In analyses controlling for all psychiatric disorders and socioeconomic status, DSH carried a 1.8-fold increased likelihood of being convicted of a violent crime; the hazard ratio was 2.1 in women with DSH (men, 1.7). The association was specific for violent crime only and held for any degree of intent or lethality of DSH. Concurrent substance use disorders significantly increased the association of DSH with violent crime.

COMMENT

Many instances of DSH are manifestations of a global dysregulation of emotionality and aggression that transcends diagnosis and that is exacerbated by substances that reduce impulse control and the delay of gratification. Considering that violence directed toward others may not always have led to arrest and conviction, the study probably underestimates the association. Patients with DSH should routinely be evaluated for risk for violence toward others as well as themselves.

Do Antidepressants Contribute to the Risk for Dementia?

Joel Yager, MD reviewing Then C-K et al. PLoS One 2017 Apr 6

In a large Taiwanese registry study, antidepressants taken for any reason were variably associated with increased dementia risk.

Depression has been associated with increased risk for dementia. Now, researchers have used the Taiwanese national health registry to examine whether antidepressant medications, independent of depression and other conditions linked to subsequent dementia, might contribute to dementia risk.

The investigators identified 5819 individuals who received antidepressant prescriptions for any reason between 2003 and 2006 on at least two occasions more than 30 days apart. Of this group, 17% were diagnosed with depression (major depression, dysthymic disorder, or depressive disorder not otherwise specified), 24% with an anxiety disorder, and 20% with insomnia; many others had assorted medical conditions considered risk factors for dementia. A comparison cohort consisted of 23,276 age- and sex-matched individuals not taking antidepressants. Records were examined through 2011 for subsequent diagnoses of dementia or Alzheimer disease.

Antidepressant use was associated with dementia risk, independent of demographics, stroke, depression, diabetes, hypertension, hyperlipidemia, insomnia, anxiety, cumulative daily dose of antidepressants, and comorbidities. Risks differed by antidepressant class (hazard ratios: selective serotonin reuptake inhibitors [n=6], 3.7; serotonin-norepinephrine reuptake inhibitor [n=1], 4.7; tricyclic antidepressants [n=3], 3.3; tetracyclic antidepressant [n=1], 6.6; monoamine oxidase inhibitor [n=1], 4.9; serotonin antagonist and reuptake inhibitor [n=1], 4.5) and were elevated with highest daily doses measured cumulatively.

COMMENT

This study lacks data on smoking, concurrent benzodiazepines, and other factors that might correlate with both antidepressant use and dementia risk. Although some studies have suggested that antidepressants spare cognitive function and offer protection against dementia, others have raised concerns similar to the present authors'. A recent systematic review and meta-analysis also found a heightened risk, notably in individuals whose antidepressant use occurred before age 65 (Depress Anxiety 2017; 34:217). While appreciating antidepressants' considerable benefits (as well as the considerable risks of untreated depression), we must undertake the important task of clarifying their long-term risks.

Adult Outcomes of First Suicide Attempts in Children Versus in Adolescents

Barbara Geller, MD reviewing Peyre H et al. J Clin Psychiatry 2017 Mar 28

In adulthood, attempters aged <13 years had higher rates of mania, hypomania, and panic disorders; greater functional impairment; and more multiple attempts than those who were aged 13 to 17.

To learn about risk for suicide attempt in children versus adolescents and subsequent outcomes in adulthood, investigators analyzed data from a U.S. epidemiological study that included in-person interviews of 34,653 adults. A first suicide attempt was made by 104 participants at age <13 years and by 415 at ages 13 to 17. Mean age of attempters at interviews was 36; >70% were women.

Before the first suicide attempt, children had higher rates of physical and sexual abuse, whereas adolescents were more likely to sustain major depression. In adulthood, the younger-attempt group had higher rates of mania/hypomania and panic disorders and worse social function than the older-attempt group. Multiple suicide attempts were more frequent among children than adolescents (61% vs. 33%). The study provided no information on suicidal methods.

COMMENT

Higher rates of adulthood bipolar disorders among the youngest attempters are consistent with prospective data showing high rates of suicidality in children with bipolar disorders. Notably, the younger attempters had abusive families and experienced traumatic parental maltreatment before the suicide attempt.

Several strategies may be useful in identifying children at risk for a suicide attempt. Clinicians should specifically ask about thoughts of self-harm because, unlike adults, children do not spontaneously share suicidal ideation. Also, children are unlikely to communicate about abuse histories in the presence of abusers, and so they should be interviewed separately from their parents.

Should We Treat Patients with Subclinical Hypothyroidism?

Allan S. Brett, MD reviewing Stott DJ et al. N Engl J Med 2017 Apr 3

In an older population, treatment was not beneficial.

Subclinical hypothyroidism (i.e., elevated thyroid-stimulating hormone [TSH] and normal free thyroxine levels) is common, but the value of treatment remains controversial. In this U.K. randomized trial, investigators identified 737 older patients (age, ≥ 65) who had laboratory evidence of subclinical hypothyroidism within the previous 3 years (TSH levels, 4.6–19.99 mIU/L) and were not treated. Patients received either supplemental levothyroxine or placebo; initial levothyroxine dose was either 25 μg or 50 μg daily, depending on body weight and cardiac history, and dosing was titrated to achieve a normal TSH level (0.4–4.6 mIU/L). At baseline, mean TSH level was 6.4 mIU/L, and mean free thyroxine level was 1.03 ng/dL.

During 1 year of follow-up, standardized thyroid symptom scores and fatigue scores (the primary outcomes) and numerous secondary outcomes — including quality of life, grip strength, and body-mass index — were similar in the two groups. No adverse effects from supplemental levothyroxine were noted.

COMMENT

One year of treatment for older patients with subclinical hypothyroidism has no obvious clinical value; whether longer duration of treatment confers benefit (or harm) remains unclear. An additional observation is notable: Of patients who initially were eligible for this trial based on past test results, about 60% had normal TSH levels when they were retested prior to randomization (such patients were excluded from enrollment). Frequent spontaneous normalization of mildly elevated TSH levels has been described previously.

Psychogenic Non-Epileptic Seizures: Clinical Issues for Psychiatrists

Omar H. Abbasi, MD and Colleagues

TABLE 1. Psychiatric comorbidities in PNES compared with ES²²

Comorbidity	Rates of comorbidity with PNES (%)	Relative risk of comorbidity when compared with ES
Total	53 - 100	1.3, statistically significant
Depression	8.9 - 85	1.6, statistically insignificant
Anxiety	4.5 - 70 (higher number from panic disorder)	1.82, statistically significant
PTSD	7 - 100	3.21, statistically significant
Personality disorders	5.4 - 74.3	1.73, statistically significant
Psychosis	0 - 15	
Substance abuse	9.8 - 29.5	

PNES, psychogenic non-epileptic seizures; ES, epileptic seizures.

Assessment and Treatment

1 Differentiate PNES from epileptic seizures using continuous vEEG monitoring. If vEEG monitoring is not available, convulsive-type PNES may be differentiated based on history and observation of the seizure episodes by a seasoned neurologist.

3 Perform a psychiatric review of symptoms, especially for PTSD.

5 Treat any comorbid psychiatric diseases appropriately with psychopharmacology.

7 Consider alternative interventions such as psychodynamic therapy and mindfulness meditation if deemed appropriate (ie, if the psychiatrist is able to identify underlying conflict or emotional dysregulation).

2 Rule out other causes such as neurocardiogenic syncope and periodic limb movements of sleep; consider factitious disorder or malingering.

4 Work with the neurology team to inform and educate patients about their disease; this may be in the form of a consult, leaflet, or psychoeducational group program.

6 Cognitive behavioral therapy is considered a first-line intervention.

TABLE 2. Six-item tool for differentiating PNES from ES²³

Item	Epileptic seizures	PNES
Eyes	Opened	Closed
Head	Fixed/unilateral	Side-to-side movements
Limbs	In phase/same direction	Out of phase
Body (axis)	Straight	Opisthotonus
Body (movement)	No rotation	Intense rotation in bed
Evolution of seizure	Continuous	Fluctuating

PNES, psychogenic non-epileptic seizures; ES, epileptic seizures.

SIGNIFICANCE FOR THE PRACTICING PSYCHIATRIST

Psychogenic non-epileptic seizures (PNES) remain a very difficult disease to diagnose and manage for psychiatrists and neurologists alike. It is our hope that after reading this article you will have a greater understanding of how to assess patients and diagnose PNES. In addition, we hope this article will shed light on the current challenges of treating such patients and enable you to develop an appropriate treatment plan.

- ▶ Always remember to screen for psychiatric comorbidities of PNES and plan treatment accordingly.
- ▶ Anti-epileptic drugs are not effective in treating PNES and may worsen symptoms.
- ▶ Approach PNES treatment with a focus on improved functioning rather than on making sure the patient is seizure-free.

TABLE 3. Summary of epileptic seizure semiology**Parietal cortex**

- “Jacksonian march”: a tingling/tightness sensation developing in a clearly defined region of the body and radiating to another region, reflecting the spreading activation of the epileptiform discharge

Visual cortex

- “Bright spots” or “dark spots”
- Ictal blindness

Temporal cortex

- Auditory auras: auditory hallucinations such as voices/tunes
- Gustatory auras: unpleasant taste, usually unable to identify the taste (associated with frontal lobe epilepsy as well)
- Psychic auras: feeling unreal/strange, “déjà vu” or “jamais vu”
- Abdominal auras: vague unpleasant feeling around the abdomen, nausea
- Automotor seizures: oroalimentary automatisms such as chewing, swallowing, and smacking lips; consciousness is usually impaired

Frontal cortex

- Most likely to be missed on scalp EEG
- Autonomic auras: tachycardia, altered breathing, sweating; clonic/tonic seizures
- Consciousness is usually preserved early in the seizure episode if seizure originates from the frontal cortex, but rarely preserved when it becomes generalized
- Versive seizures (specifically the frontal eye field): sustained unnatural turning of the eyes/head
- Hypermotor seizures: preserved consciousness, with large/violent movements that may be asynchronous, frequently leads to an erroneous diagnosis of PNES
- Duration of seizure: usually less than 1 minute

Although psychogenic non-epileptic seizures (PNES) are events that appear to be similar to seizures, they are not caused by abnormal electrical brain activity. Instead, they are thought to have an underlying psychological cause.

PNES is classified as a subtype of conversion disorder under the category, somatic symptom and related disorders in DSM-5. When coding for PNES as a conversion disorder using ICD-10, the diagnosis must include the specifier “with attacks or seizures” (ICD-10 code F44.5) to differentiate it from other conversion symptoms (eg, dysarthria, sensory loss), which are coded separately. Alternate names frequently used for PNES are non-epileptic attack disorder, functional seizures, stress seizures, psychogenic seizures, and pseudoseizures. The last has largely fallen out of favor because of the pejorative nature of the term “pseudo,” which may imply that the symptoms are not real and therefore undermine the impact of the disorder on a patient’s life. It is not uncommon to see both PNES and epileptic seizures in the same patient.

PNES has a long history in the medical literature, where it has been described by several aliases, the most common being hysteria. Equally as varied were the many hypotheses for the causes of hysteria. Because of its observed frequency in females, hysteria was conceptualized as the result of a “wandering uterus” that had been displaced in the body and subsequently inhabited other organs and appendages, applying pressure and leading to the manifestation of physical symptoms. This theory eventually lost prominence as symptoms of hysteria were increasingly reported in males.

Related content: Update on Psychogenic Nonepileptic Seizures

In the 19th century, the phenomenon became a passion of French neurologist Jean Charcot, who identified it primarily as a neurological disorder with psychological underpinnings that could, in some cases, be treated by hypnosis. Sigmund Freud, after studying under Charcot, theorized the symptoms as a conversion of repressed libidinal impulses into physical form, which brought about its current title of conversion disorder. Alternatively, Pierre Janet suggested hysteria was more of a dissociative phenomenon that occurred at times of stress with the purpose of allowing an individual to re-experience a traumatic event while separating the memory from conscious awareness.

Assessment

Clues to a possible diagnosis of PNES can be discovered by eliciting a seizure history including onset, typical semiology of the seizure, and treatment. Patients with PNES are likely to have seizures more frequently with more hospital visits than patients with epilepsy. They may often carry a diagnosis of refractory epilepsy, and it is not uncommon for patients to have current or past prescriptions of antiepileptic drugs. Antiepileptic drugs, however, are not effective in treating PNES and may either worsen the symptoms or cause only a transient partial response.

Psychiatric comorbidity is quite common in patients with PNES. The most frequently co-occurring disorders are PTSD, anxiety disorder, personality disorder, and depression (**Table 1**). Patients with comorbid psychiatric disorders may also have more severe dysfunction and higher levels of stress. Identifying a comorbid psychiatric condition can result in more specific treatments that target those symptoms as well as better outcomes for patients.

In addition to performing a psychiatric review of systems, inquire about any history of medically unexplained symptoms (hand tingling, paralysis, etc) and screen for possible somatoform disorders. Patients with PNES may frequently report pain as other somatic symptoms. Prescriptions for pain medication were found to have a positive predictive value of 76.9% in patients with PNES compared with patients with epilepsy.

Attempts to identify typical psychological features of PNES have been largely unsuccessful. *La belle indifférence*, coined by Freud in his observation of patients with conversion disorder, has been thought to be a classic characteristic; however, a systematic review of the literature found this feature was observed in only a minority of those with conversion disorder and not at a significantly higher rate than in controls. Alexithymia was thought to be more common in this patient population but has been found to occur at similar rates in patients with PNES and in patients with epilepsy or other medical disorders. Patients with PNES can be divided based on problems with emotional regulation: one group has a tendency toward emotional dysregulation, and the other is emotionally over-regulated.

The precipitating psychological stressor criterion to confirm a diagnosis of PNES was removed from the criteria for conversion disorder in DSM-5. Rates of precipitation trauma are between 44% and 100% in patients with PNES; however, most patients do not report a trigger or stressor during the initial psychiatric assessment. That is not to say traumatic factors will not be discovered once the patient engages in treatment. Lifetime physical and sexual abuse in particular are reported at rates of 23% to 77% and childhood sexual or physical abuse at 32.4% to 88%. Outside of abuse, bereavement and being in or witnessing an accident are other possible antecedent factors. Early-onset (adolescence) PNES has been associated with bullying; late-onset PNES has been associated with health-related trauma.

When assessing triggers, keep in mind that one-third of epilepsy patients also report childhood physical or sexual abuse. Moreover, stress can trigger epileptic seizures.

Diagnosis

The gold standard for diagnosing PNES is continuous video electroencephalography, or vEEG. This should be done only after carefully eliciting a description of the typical seizure presentation, also known as semiology, from the patient or a family member. Only a video recording that captures an episode resembling the reported semiology with no concomitant epileptiform activity

seen on EEG (vEEG) can be used to make a definitive diagnosis. If multiple seizure types are reported, then each type of seizure should be visualized on vEEG because of the possible co-occurrence of PNES with epileptic seizures.

vEEG usually requires inpatient admission to an epilepsy monitoring unit, which is not found at all hospitals. Such admissions are also costly and may have long wait times. However, a routine EEG that lasts 20 to 30 minutes has a 1% chance of capturing even an epileptic seizure and is an insufficient substitute. Ambulatory EEG has also not been shown to be a reliable diagnostic test for PNES. The Nonepileptic Seizures Task Force for the International League Against Epilepsy published a staged diagnostic approach to PNES. Some of their recommendations are reviewed here; however, we encourage readers to refer to the article for a more comprehensive review.

When vEEG is not available, a seasoned clinician could possibly diagnose PNES by observing specific semiology alone. Bedside tools based on data from several studies have been created to aid in visual diagnosis of PNES episodes (**Table 2**). However, the studied semiologic differences are specifically between convulsive-type PNES and generalized tonic-clonic (GTC) seizures. PNES as well as epileptic seizures have various presentations (eg, absence seizures, frontal seizures) that significantly reduce the ability to diagnose PNES by observation alone and can lead to misdiagnosis. In such cases, a push for vEEG referral by the consulting psychiatrist is warranted.

In regards to observed semiologic differences, convulsion-type attacks in PNES tend to be asymmetrical and asynchronous, have a more fluctuating inconsistent course, and may respond to bystander intervention. Preserved awareness during events, especially with bilateral limb movements, should raise suspicion for PNES. Pelvic thrusting has been observed more frequently in PNES; however, it can occur in GTC seizures as well. Side-to-side head and body movement along with eye and mouth closure have been more readily associated with PNES than with GTC seizures. Urinary incontinence and tongue biting have not been shown to be useful in differentiating PNES from GTC seizures. The latter rarely last more than 2 minutes.

Post-ictally, patients with PNES are more likely to regain awareness quickly, recall the seizure event, and not have symptoms of fatigue or headache. PNES episodes are also more typically followed by rapid shallow breathing that quickly subsides, whereas GTC seizures are frequently followed by prolonged harsh, loud, deep breathing.

Non-epileptic status, a prolonged episode of seizure-like symptoms that lasts more than 30 minutes, was reported by one-third of patients in one study. However, unlike status epilepticus, non-epileptic status does not pose an imminent risk of brain injury.

Along with semiology, there are a handful of soft signs that may heighten suspicion of PNES. One is the teddy bear sign, in which an adult patient keeps a stuffed animal in the hospital bed.

The specificity of this soft sign was rated highly by a retrospective chart review. However, a prospective study that looked at the presence of a stuffed animal at the time of admission in 264 patients found that of the 34 patients who presented with a stuffed animal, 56% had a diagnosis of epilepsy and 39% had a diagnosis of PNES, which gives the sign poor predictive value.

Another soft sign for PNES is the number of allergies a patient reports. Independent of other risk factors, patients who reported more than 12 allergies had a 6-fold higher likelihood of a PNES diagnosis.

Differential diagnosis

As mentioned above, one of the conditions in the differential diagnosis of PNES is epilepsy. **Table 3** summarizes various sites of seizure origin and likely semiology. (For a more complete description of epileptic semiology, see the article by Noachtar and Peters.)

Another condition in the differential may be periodic limb movements of sleep, which are highly correlated with restless legs syndrome. They occur only during sleep with very repetitive, stereotyped limb movements; are more likely to involve the lower extremities; and can be bilateral.

Up to 13% of patients who are referred to an epilepsy clinic may have neurocardiogenic syncope, a syndrome that can mimic epileptic seizures. There are multiple precipitating factors, one of which is emotional stress. On rare occasions, patients can have seizure-like activities during syncopal episodes. Patients would likely lose consciousness first and fall before uncontrolled muscle movements.

Factitious disorder and malingering

It is important to recognize when seizure-like symptoms are being volitionally produced for the purpose of maintaining a sick role or for secondary gain. Unfortunately, vEEG may not be able to separate conversion disorder from factitious disorder. However, a study that looked at the possibility of physical symptoms in PNES serving as an unconscious motivation to acquire “the sick role” found that there were no differences between patients with PNES and controls in attitudes toward illness or the desire to be sick.

While the desire to maintain a sick role in factitious disorder may be unconscious, the act of deception itself is conscious and purposely perpetrated. Clinical scenarios that may heighten suspicion of factitious disorder are those where the symptoms seem to occur or increase in severity when requests for unnecessary interventions are declined by the treatment team. Another example is a sudden increase in seizure frequency when a patient is informed that discharge from the hospital is imminent.

Prognosis

The prognosis of the disorder, like its etiology, is varied. With no intervention, slightly more than one-third of 260 patients with PNES were seizure-free at 1-year follow-up. Psychological factors that predict poor prognosis include dissociative tendencies, somatization, negativism, and depression. Keep in mind, however, that seizure frequency may not always correlate with quality of life, and patients who are seizure-free with untreated comorbid psychiatric disorders may be as impaired as those who continue to experience seizures.

Patients with PNES who receive the diagnosis without any intervention continue to be high health care utilizers; however, the chief complaint becomes pain rather than seizures. The frequency of total outpatient visits, while also unchanged, shifts in specialty with patients having frequent visits to outpatient psychiatry clinics rather than neurology. Having an internal locus of control and being currently employed were the 2 factors found to predict a reduction in health care utilization.

Treatment

There has been a recent focus on psychoeducation and cognitive behavioral therapy (CBT) as primary methods for first-line interventions in patients with PNES. Most of the available small randomized clinical trials have shown positive results. There is also some evidence for the effectiveness of psychodynamic and mindfulness-based therapies. These specific forms of intervention may be useful if either first-line intervention is not effective or the evaluating psychiatrist deems it appropriate given the underlying psychological stressor.

Research into pharmacological treatment for PNES has focused on SSRIs as first-line treatment. LaFrance and colleagues randomized 34 patients to CBT only, CBT with flexible-dose sertraline, antidepressant only, and treatment as usual. Patients in the CBT-only group and the CBT-plus-flexible-dose-sertraline group showed a significant reduction in seizure frequency. In another study comprising 38 patients, LaFrance and colleagues found no statistical difference in the SSRI group and placebo group in seizure reduction. However, a within-group analysis showed a 45% reduction in seizure events in the SSRI group at 12 weeks.

The results from a small (N = 19) open-label, 5-month prospective study of patients with PNES showed that venlafaxine reduced the number of seizures by more than 50% in 15 patients with an average dose of 189.71 mg daily. It should be noted that participants with psychiatric comorbidities were not excluded from SSRI studies.

There is a possibility that the use of antidepressants in PNES could improve outcomes by treating comorbid psychiatric issues rather than by having a direct effect on PNES. The quest for

a pharmacological solution for PNES will have to continue. Much more research is needed before we have a first-line pharmacological treatment specifically for PNES.

Conclusion

While there have been strides over the years in our ability to diagnose PNES, its etiology and treatment remain elusive. It is imperative, however, that psychiatrists assist in early diagnosis and treatment interventions to decrease the severity of burden from this disorder. The current empirical studies may help us discover what Charcot alluded to in his anecdotal experiences—that PNES may be a symptom of a variety of mental and biological processes rather than a specific disorder unto itself, requiring personalized treatments instead of a one-size-fits-all intervention. The goal for PNES treatment may also not be the complete elimination of seizures, but rather a focus on seizure reduction and patient functioning.

Dr. Mubin:

Conversion disorder symptoms, including psychogenic non Epileptic seizures respond very well to hypnosis. In addition counseling of patient and family is essential to remove stress in the family or outside.

Update on Medical Catatonia: Highlight on Delirium

Jo Ellen Wilson, MD, MPH and Colleagues

SIGNIFICANCE FOR THE PRACTICING PSYCHIATRIST

The article highlights important aspects of catatonia in medical patients, particularly new information on the co-existence of delirium with catatonia. We stress that treatment of delirium with catatonia may differ from the general treatment of delirium without catatonic features.

- ▶ Delirium and medical catatonia are brain dysfunctions linked to medical conditions and may coexist with overlapping signs.
- ▶ Medical catatonia usually responds to lorazepam, the standard initial treatment for non-medical catatonia; memantine or amantadine may be helpful for augmentation.
- ▶ ECT may salvage severe and persistent cases, but the potential benefit must be weighed against the risks, especially in medically compromised patients.
- ▶ While atypical antipsychotics with benzodiazepines have been considered for psychiatric catatonia in those without fever or autonomic signs, there is no evidence that these agents are safe or effective for medical catatonia or delirium with catatonia.

TABLE. Catatonia due to another medical condition or substance¹²

Medical conditions	Substances that can induce catatonia
<ul style="list-style-type: none"> • NMDA-receptor encephalitis • Paraneoplastic limbic encephalitis • Systemic lupus erythematosus with or without cerebritis • Seizures • Encephalitis lethargica • Herpes simplex encephalitis • Subacute sclerosing panencephalitis • Neurosyphilis • <i>Borrelia burgdorferi</i> infection and sequelae • Typhoid fever • Adenovirus infection • Disseminated neurocysticercosis • HIV infection and sequelae • Intracranial mass lesions • Multiple sclerosis • Uremic encephalopathy • Posterior reversible encephalopathy syndrome • Glucose-6-phosphate dehydrogenase deficiency • Vitamin B12 deficiency • Hyponatremia • Takotsubo cardiomyopathy • Wilson disease 	<ul style="list-style-type: none"> • Tacrolimus, even at normal levels • Cyclosporine • Corticosteroids • Fluoroquinolones • Beta-lactam antibiotics • Azithromycin • Disulfiram • Dopamine antagonists • GABA-ergic agonist withdrawal • Baclofen exposure/withdrawal • Cocaine intoxication • MDMA "ecstasy" intoxication • Methylphenidate intoxication • Phencyclidine intoxication • Methoxetamine intoxication

NMDA, *N*-methyl-*D*-aspartic acid; GABA, gamma-aminobutyric acid; MDMA, 3,4-methylenedioxymethamphetamine.

Catatonia, described in 1874 by K. L. Kahlbaum, is a distinct and heterogeneous neuropsychiatric syndrome, with both motoric and behavioral signs. It may be hypokinetic, hyperkinetic, or mixed and includes volitional signs, such as mutism, negativism, and automatic obedience. It was formerly relegated to a schizophrenia subtype, or considered extinct after the advent of modern psychopharmacology. Renewed interest and emerging systematic data have highlighted the frequency and pattern of catatonic presentations in psychiatric and medical settings, including in critical illness.

Assessment

Historically, up to 40 signs were recognized, and most are now included in the published scales for detecting and rating the severity of catatonia. The Bush-Francis Catatonia Rating Scale (BFCRS) is widely used in both clinical and research settings, shows high inter-rater reliability and favorable sensitivity and specificity, and was validated in a mixed medical and psychiatric sample. The 23-item BFCRS was derived from classic descriptions of catatonia and modern diagnostic criteria. Cases are defined by the presence of 2 or more of the first 14 signs.

DSM-5 criteria require 3 or more from a similar list of 12 common catatonic signs. The BFCRS or DSM-5 items identify diverse clinical features, including motoric, behavioral, volitional, and autonomic signs. Statistical analyses identified subtypes of catatonia, including a retarded and an excited form. Malignant catatonia—a severe form with fever and autonomic instability—is uncommon but is important to identify as it may be fatal if not recognized and aggressively treated.

Despite effective treatments, patients with any form of catatonia remain at risk from serious complications such as dehydration, muscle breakdown, aspiration, or embolic phenomena. Once catatonia is recognized, these risks can be mitigated by effective treatments. Among the most studied treatment modalities, regardless of the underlying etiology, prompt administration of gamma-aminobutyric acid (GABA) receptor agonists or ECT for severe or resistant cases usually relieves the symptoms and may be lifesaving.

Pathology of catatonia in the context of medical illness

The exact pathogenesis of catatonia remains unknown. Systematic examination of catatonia with genetic and brain imaging studies has been slow to develop. Familial aggregation has been reported for periodic catatonia, and preliminary evidence associated this with 15q15 chromosome. Single photon emission CT studies using a GABA-A ligand revealed reduced binding in areas of the frontal lobe. More recent studies showed increased cerebral blood flow in the supplementary motor cortex, which correlated with BFCRS severity scores, and apparent loss of frontal and insular gray matter in catatonic schizophrenia.

Related content. Mini Quiz: Medical Catatonia

For catatonia in medical populations, the pattern or frequency of catatonic signs does not distinguish psychiatric from medical catatonia. A review of case reports on catatonia associated with brain lesions found an association with frontal and basal ganglia damage. The most recent systematic reports of medical catatonia confirm that non-localizing encephalopathies were the most common primary diagnoses associated with catatonia; a variety of non-specific EEG findings were also seen. Catatonia is generally thought to be under-recognized in the medically ill.

Catatonia and delirium

Of particular interest and potentially of great clinical significance is the relationship between catatonia and delirium. Delirium is the classic syndrome of acute brain dysfunction—with disturbed attention, awareness, and cognition—and is predictive of excess mortality, longer hospitalization, costlier care, and long-term cognitive impairment. While delirium is often assessed in critical settings such as the ICU, catatonia is not. Recognition and study of ICU catatonia have until recently been hindered by recent editions of DSM, which consistently hold that catatonia cannot be diagnosed in the presence of delirium. However, there is no clear evidence to support the exclusion.

Despite the DSM exclusion, delirium might coexist with catatonia, perhaps most prominently in the hypoactive motoric subtype of delirium. Hypoactive delirium includes decreased motor activity, decreased speech, and behavioral withdrawal—all of which map to catatonic features.

The first prospective report of catatonia with delirium was published in 2014. The data showed that 13% of 205 consecutive delirium cases met DSM-5 criteria for catatonia, and 32% met BFCRS criteria for catatonia. However, no treatment or outcome data were presented.

The many implications of more clinical attention and systematic study of comorbid delirium and catatonia include prognosis and management. For catatonia, active treatment consists of benzodiazepines (typically lorazepam) and/or ECT; antipsychotics are generally avoided because they may worsen catatonia or precipitate a lethal or malignant form similar to neuroleptic malignant syndrome (NMS). Conversely, treatment of delirium addresses the underlying medical condition and environmental factors, and antipsychotics are often used; however, benzodiazepines are generally avoided (except for known substance-withdrawal delirium).

There are no prospective data on the management or outcome of catatonia with delirium that address this apparent dilemma. However, a recent study of medical inpatients identified 54 cases of catatonia of whom 43% had a prior psychiatric history, while 54% had suspected delirium. When medical catatonia was compared to that attributed to psychiatric disorders, there

was no statistical difference in the rates of treatment attempts using lorazepam nor in response, which was greater than 80%. However, cases of catatonia comorbid with suspected delirium were less likely to respond to lorazepam (71%) than cases without delirium (100%), regardless of etiology. While this was a retrospective study, it supports the assertion that catatonia and delirium can be comorbid and suggests that in many cases the treatment of catatonia with benzodiazepines may be successful in the presence of a delirium.

Differential diagnosis

A variety of medical conditions can produce stupor, which is a decreased awareness and interaction with the external environment. Stupor can occur with preserved alertness, more often seen in catatonia, or with lethargy, more often seen in delirium. Stupor that is associated with a metabolic disorder or that is associated with delirium may present with catatonic features. The **Table** presents examples of medical conditions associated with catatonia.

NMS, serotonin syndrome, and non-convulsive status epilepticus are other examples of stuporous states associated with catatonia. It may be that NMS and serotonin syndrome are actually medication-induced malignant catatonia.

Delirious mania is a rare syndrome linked to bipolar disorder characterized by the rapid onset of delirium, mania, and psychosis, with prominent hyperactive catatonia. Delirious mania can be construed as a malignant hyperactive form of catatonia, as well as a hyperactive delirium. Delirious mania has been associated with medical disorders. The newly characterized excited delirium syndrome, induced by cocaine or other stimulants, has been likened to delirious mania. Delirious mania was reported after cerebellar/pontine stroke, which produced delirium that was treated with antipsychotics that led to a catatonic state; this ultimately resolved with continuation of valproate, removal of antipsychotics, and administration of lorazepam.

Treatment strategies

Differences between etiologies (psychiatric vs medical) do not appear to alter the general treatment approach for catatonia. Removal of suspected offending agents, treatment of the underlying medical condition, or management of drug withdrawal are essential for both forms of catatonia.

For persistent catatonia, rapid initiation of lorazepam or a related benzodiazepine, which may require cautious titration to higher dosages (eg, 8 mg/d or more of lorazepam), usually leads to improvement of symptoms. Benzodiazepines (and related agents such as amobarbital and zolpidem) may counteract hypothesized GABA-receptor hypofunction in catatonia. Intravenous lorazepam has more assured absorption and may exert more prolonged clinical effects than the oral form based on differing drug distribution.

Potential adverse effects of high-dose intravenous lorazepam include anion gap acidosis from its solvent, propylene glycol. This risk increases with higher doses and in renal impairment, but toxicity has been reported with as little as 2 mg per hour. The osmolar gap (a marker for glycol toxicity) should be monitored every other day if the lorazepam infusion reaches 1 mg/kg daily.

Augmentation with memantine or amantadine may also be helpful. Their hypothesized mechanism is N-methyl-d-aspartic acid (NMDA) receptor antagonism, which may be linked to GABA hypofunction. Memantine can be started at 5 to 10 mg daily and titrated based on medical status with monitoring of the QT interval. Improvement from memantine seems slower than with lorazepam, but both can be co-administered. Amantadine is started at 100 to 200 mg daily and titrated, but it should be used with caution if renal impairment or seizure risk is present. Mania, suicidal ideation, and withdrawal-emergent NMS have also been reported with administration of amantadine.

ECT can be considered for inadequate medication response for persistent and severe catatonia and may be used more emergently for malignant features (autonomic instability and hyperthermia). Use of ECT for catatonia in medical settings or with uncertain CNS pathology should be approached cautiously, and the potential benefit weighed against the known adverse risk of severe and prolonged catatonia. Some reports show a benefit of ECT for catatonia for various acute neurological illnesses. However, no benefit was seen with the use of ECT in catatonia after cerebral hypoxia; in this setting, it may worsen neurological status.

Atypical antipsychotics were reported to benefit some cases of non-medical catatonia after other treatments had failed, or for coexistent catatonia and psychosis when ECT was not feasible. Serum iron should be measured, since low levels may be predictive of conversion to malignant catatonia. Benzodiazepines should be continued concurrently with the antipsychotic, with monitoring for extrapyramidal or autonomic symptoms that portend malignant catatonia or NMS. Antipsychotics in medical catatonia or delirium with catatonia have not been studied, and caution is advised with their use.

Collaboration with medical services

When medical catatonia is identified, the primary hospital service may initially resist lorazepam treatment, particularly when the patient is medically compromised. Under-dosing of lorazepam and treatment failure may result if the rationale for its use is not clearly expanded. Inviting the primary care team to witness a lorazepam or zolpidem challenge may help medical specialists appreciate that a sedating agent can improve catatonic stupor.

Frequent vital sign assessments, monitoring of the osmolar gap, and pulse oximetry can improve safety, along with ready access to flumazenil for reversal of potential adverse effects of

benzodiazepines. If sedation is a concern, adding non-sedating memantine or amantadine may allow for lower benzodiazepine dosing.

When multiple hospital consultants are involved in complex cases, interdisciplinary meetings are strongly recommended. In such situations, we encourage a clear consensus that identifies specific targets for defining both treatment response and adverse effects.

Dr. Mubin – Injection Lorazepam is not available in Pakistan. Inj. Haloperadol 10mg every hour is also quite effective.

Doctors and Marriage: Should You Have a Prenuptial?

Discussion in 'Doctors Cafe' started by Nada El Garhy

Introduction

Despite the horror stories about ugly breakups among doctors, physicians in the United States are actually more likely to stay with their spouses than other white-collar professionals, including lawyers and other non-healthcare workers. Among healthcare professionals in particular, with the exception of pharmacists, physicians are less likely to get divorced than dentists, nurses, and healthcare executives.

These findings, which were published in February 2015 in the BMJ, included responses from nearly 49,000 doctors.

While this is certainly encouraging news given the very demanding schedules many physicians keep, the reality is that any divorce can prove to be an expensive proposition for everyone involved.

But there's a way to lessen the financial pain of a breakup, if not the emotional sting: a prenuptial agreement, or a "prenup."

Take the case of a 45-year-old surgeon in New Jersey who was preparing for his upcoming wedding. This would be his second marriage after having been divorced for 7 years. His colleague reminded him about a former partner who had lost half of his sizable investment in his medical practice during his divorce. Disturbed, the surgeon called his attorney to ask his advice. The lawyer's response was unequivocal: "Ask her to sign a prenup."

While no one enters a marriage expecting to split up, the reality is that almost 1 in 3 first marriages ends in divorce -- as do nearly one half of second or third ones. Your best opportunity

to protect yourself is before you tie the knot. Otherwise, you may find yourself embroiled in a legal battle with dueling experts trying to value your practice both at the time of your marriage and your later divorce.

To be sure, few things throw cold water on a courtship more than the mention of a prenup. But as a high-earner -- or a potential high earner -- it may make sense to try to protect as many of your assets as the law, through a carefully considered prenuptial agreement, will allow.

Before you dismiss the idea as a romance-killer, consider that your future spouse may be bringing a great deal of assets to the marriage and may also want such a contract for his or her own protection as well.

Let's examine the pros and cons of prenups for physicians and their betrothed, using 2 basic scenarios.

Young Doctors, First Marriage

If this is your first marriage and you're not bringing a lot of debt or assets to the union, you may not need a prenuptial agreement, experts say. But for everyone else, including a doctor who has recently started or is thinking of starting his or her own practice, a prenup could make sense, especially since the stigma around them is starting to fade (albeit slowly).

"Prenuptial agreements are becoming more generally accepted as an effective way to protect assets. They're no longer limited to a specific gender or age group," says Marlene Eskind Moses, a past president of the American Academy of Matrimonial Lawyers (AAML) and a principal with MTR Family Law, in Nashville, Tennessee. In fact, a 2010 survey of AAML members revealed that women are becoming more likely than men to initiate a request for a prenup and that the overall number of prenups is on the rise.

Part of the reason, experts say, is that people are waiting longer to get married, meaning they may have more assets -- and big debts, such as credit card balances, mortgages, and student loans -- to bring to the union than couples who wed when they're much younger. A prenup can help you preserve those assets (or sidestep those debts) in the event of a divorce.

Same-sex couples may also benefit from a prenup, even if their state doesn't legally recognize the union. That's because prenuptial agreements are general legal contracts, which, like any contract, any 2 parties are free to enter into.

Laws Vary by State

Moreover, without a prenuptial agreement, you could be subject to the laws in your state -- at least 9 of which require a straight 50-50 split of assets accumulated during the marriage, as Steven Spielberg discovered in California. Spielberg and his first wife, actress Amy Irving, didn't have a legally enforceable prenup -- it was written on a cocktail napkin (yes, a cocktail napkin)

and there were no witnesses -- so Spielberg was forced to cough up one half of his net worth (a whopping \$100 million) when they divorced after 4 years of marriage.

In all others states (with the exception of Alaska, which is a mixed bag), a judge will consider what's fair in the absence of a prenup, on the basis of such factors as the couple's ages, the length of the marriage, the number of kids involved, and the role of each spouse in building household wealth. A wife who supported her husband financially as he went through medical school, for instance, may be entitled to a much more generous settlement because of the sacrifices she made while he pursued his dream.

"Sometimes the very reason for a prenup is to protect the non-monied spouse," says Ginita Wall, a financial planner in San Diego, California; coauthor of the book *ABCs of Divorce for Women*; and cofounder of the Women's Institute for Financial Education, a nonprofit dedicated to improving women's knowledge of finances. "We had a client who made \$4000 to \$5000 a month selling real estate, and she wanted to be compensated for that lost income if she agreed to marry him and become a stay-at-home mom.

"When the couple broke up some 20 years later, she received all of that lost income as part of her divorce settlement, thanks to the prenup. She took some of that money and used it to help her daughter pay for college."

Although we've discussed tangible assets to this point, prenuptial agreements can also be used to hammer out lifestyle issues, including what religion any future children will be raised in and whether they'll attend public or private schools. (Custody and child support issues are determined separately by the courts, so they can't be added to a prenup.)

Older Doctors, Second (or Third) Marriage

"As more people marry or remarry in their later years, there's an increasing emphasis on protecting pensions and retirement benefits if the marriage doesn't work out," says family law attorney Marlene Eskind Moses. Plus, there are often kids involved in second marriages, as well as older parents who may need expensive care, so couples rightfully want to protect these interests as well.

Experts also say that doctors who own their own practice would be very wise to have a prenuptial agreement, especially if they built up substantial equity in it before getting engaged. The contract covers the physician, but it also protects the partners from the hassles of divvying up property in a split.

"We had a situation in a 4-doctor practice where the other 3 doctors insisted that their partner, who was getting remarried, get a prenup," recalls Gary N. Skoloff, a family law attorney with Skoloff & Wolfe, in Livingston, New Jersey. "A few years earlier, the practice had been turned upside down during his divorce proceedings by accountants who spent a year going through

receipts and other paperwork in attempting to properly value the doctor's stake in the practice. And the partners sure as heck didn't want to go through that again!"

In a case like this, where a doctor has an equity stake in the practice and wants to remarry, a prenup can protect his or her interest in the practice both before and after the marriage, says Skoloff's partner, attorney Jonathan W. Wolfe. "Without a prenup, in most states the appreciation in the value of the practice will be considered a marital asset, unless it's protected by a prenup," Wolfe says. This can lead to even greater problems in a future divorce, he explains, because "the business will have to be valued both at the time of the marriage and at the time of the divorce."

Emotional Comforts and Discomforts

Prenups are all well and good in theory, but what if your sweetie refuses to sign the document?

"That happens," Ginita Wall says, "and I've seen engagements broken off because of it. Or the person who wanted the prenup gives in and abandons the idea. The third thing that can happen, and it often does, is that the couple agrees to modify the prenup and come to terms they can both live with."

Even if you and your fiancé(e) don't think a prenup is necessary, don't be surprised if someone else nudges you to sign one. That's becoming increasingly more likely these days, lawyers say, because parents sometimes own investment properties or businesses with their children and don't want to see the new spouse possibly inherit something they had earmarked for their son or daughter.

"A prenup in a second marriage is really important," Gary Skoloff says. "By shielding certain assets, it can actually help preserve and enhance the new relationship. Everyone is immediately comfortable with one another because they know their interests are protected."

Will a Prenup Hold Up in Court?

No prenup is bulletproof, much as both spouses would like to believe. "A lawyer can't guarantee that a prenup will be enforced any more than a doctor can guarantee the result of a surgery," Skoloff cautions. Many states, for instance, require both parties to disclose all of their assets and liabilities for the prenup to be enforceable. Judges don't take kindly to folks who try to hide things.

Other circumstances, too, can put the agreement on thin ice, such as an unexpectedly large windfall (an inheritance or lottery winnings, perhaps). The key here is that the circumstances weren't foreseeable at the time the agreement was signed, making it less likely that a judge would enforce it.

Oddball lifestyle clauses, such as stipulating sex 3 times a week or that your future spouse maintain a certain weight, can also sink a prenup. The more lifestyle clauses you add, the less likely your contract is going to be enforceable. Life isn't linear, after all.

"Unfortunately, there's not a lot of uniformity to the laws on prenuptial agreements, like we have with estates or child support," says Ginita Wall. "That's why I tell people that if they move to another state and they haven't modified their prenup, don't be surprised if a judge rules on it very differently from what you'd expected."

You'll increase the chances of a prenuptial agreement being fully enforceable if both parties retain their own separate legal counsel and sign the document well in advance of the chime of wedding bells, so that no one can argue it was agreed to under duress.

"This shouldn't be handled like your typical negotiation, where both parties ask for the moon and then agree to meet in the middle," Jonathan Wolfe says. "It's better if both people are reasonable up front and are open and honest about their objectives. No one wants to mess up what's already a good relationship."

Conclusion

The decision to enter into a prenuptial agreement is a highly personal one, layered with emotion. If you're young and just starting out -- and you and your fiancé(e) have roughly equal assets -- you probably don't need one. But an older doctor, with children from a previous marriage and significant assets, may want to consider the extra measure of financial protection that a well-crafted prenup can afford.

Pharmacotherapy for alcohol use disorder

Bankole A Johnson, DSc, MD and Colleagues

INTRODUCTION — The World Health Organization estimated that more than 75 million people had alcohol abuse or dependence worldwide over a 12 month period. Nearly two million deaths each year have been attributed to the disorders. The prevalence of alcohol use disorders in primary care ranges from 20 to 36 percent, although the conditions are frequently untreated.

Psychosocial interventions are effective in the treatment of alcohol abuse and dependence; however, as many as 70 percent of individuals relapse after psychosocial treatment alone. Several medications can be used to treat alcohol use disorder, leading to reduced heavy drinking and increased days of abstinence. There is little evidence on the effectiveness of medication in the treatment of nondependent alcohol abuse.

The psychiatric diagnoses, alcohol abuse and alcohol dependence, in DSM-IV-TR were replaced by one diagnosis, alcohol use disorder, in DSM-5. Although the crosswalk between DSM-IV and DSM-5 disorders is imprecise, alcohol dependence is approximately comparable to alcohol use disorder, moderate to severe subtype, while alcohol abuse is similar to the mild subtype.

This topic focuses on medication in the treatment of alcohol use disorder. The epidemiology, pathogenesis, clinical manifestations, assessment, and diagnosis of alcohol use disorder, as well as psychosocial treatments for the disorder, are discussed separately. (See "Risky drinking and alcohol use disorder: Epidemiology, pathogenesis, clinical manifestations, course, assessment, and diagnosis" and "Psychosocial treatment of alcohol use disorder" and "Screening for unhealthy use of alcohol and other drugs in primary care" and "Brief intervention for unhealthy alcohol and other drug use: Efficacy, adverse effects, and administration".)

NEUROBIOLOGY — Pharmacologic treatment of alcohol use disorder has mostly focused on altering the reinforcing effects of alcohol use. Medication development has focused on several neurotransmitter systems that interact with the corticomesolimbic dopamine (CMDA) pathway, which can mediate reinforcement. Many available or promising compounds appear to act by modulating the function of opioids, glutamate (with or without gamma aminobutyric acid, GABA), and serotonin (5-HT).

Some alcohol-dependent individuals possess a biological predisposition to the disease. These biologically vulnerable alcoholics may benefit from specific adjunctive medications addressing the underlying abnormalities.

TREATMENT PRINCIPLES AND OVERVIEW

Indications — Nearly all clinical trials finding medications efficacious for alcohol use disorders studied recently abstinent patients with a DSM-IV-TR diagnosis of alcohol dependence. Applying these findings to patients diagnosed under DSM-V is imprecise, but the most closely comparable group of patients are those with alcohol use disorder, moderate to severe subtype (ie, patients with four or more symptoms within a 12-month period). DSM-V criteria for the diagnosis of alcohol use disorder are described separately. (See "Risky drinking and alcohol use disorder: Epidemiology, pathogenesis, clinical manifestations, course, assessment, and diagnosis".)

Pharmacotherapy should be used in patients with alcohol use disorder, moderate to severe subtype, who:

- Have current, heavy use and ongoing risk for consequences from use
- Are motivated to reduce alcohol intake
- Prefer medication along with or instead of a psychosocial intervention
- Do not have medical contraindications to the individual drug

Most data on the efficacy of pharmacotherapy are not generalizable to patients with the mild subtype of alcohol use disorder. Patients with a mild subtype alcohol use disorder who are currently drinking heavily and risk serious consequences can be considered for these treatments on a case-by-case basis.

Goals — The traditional goal of treatment for alcohol use disorder is abstinence, which remains a primary treatment focus. In addition, reduction of heavy drinking has become accepted as an alternative treatment goal. The frequency of heavy drinking (defined as more than five drinks per day for men and four for women) shows the highest correlation with negative life consequences such as impaired driving, interpersonal problems, and injuries. Reduction of heavy drinking may be a more acceptable goal for some patients who lack readiness to quit drinking.

Initiation and duration — Pharmacologic treatment for alcohol use disorder is often initiated during hospitalization for alcohol intoxication or withdrawal. (See "Ambulatory management of alcohol withdrawal" and "Management of moderate and severe alcohol withdrawal syndromes".)

Naltrexone can be initiated while the individual is still drinking. This permits treatment for alcohol use disorder to be provided in community-based practice at the point of maximum crisis without the need for enforced abstinence or detoxification. Disulfiram, which by intent leads to adverse effects when combined with alcohol intake, should only be used by abstinent patients in

the context of treatment intended to maintain abstinence. Research indicates that acamprosate should be used once abstinence is achieved.

After initiating medication treatment, follow-up visits should be sufficiently frequent to provide the patient with encouragement and support, to engage family members if helpful, and to monitor the patients for treatment response, side effects, medication adherence, and early signs of relapse, which can lead to serious complications.

The optimal duration of pharmacotherapy is not known. Most trials studied the effect of treatment over two to six months. Experts recommend at least six months of medication with an additional six months of follow-up. The efficacy of medication treatment wanes once medications are discontinued. Of the medications described below, only topiramate requires a taper to discontinue, over a two-week period.

FIRST-LINE MEDICATIONS — Naltrexone cannot be given to patients taking opioids. If opioids are required to treat pain, naltrexone should be discontinued. Naltrexone is contraindicated in acute hepatitis or liver failure.

Oral naltrexone — Naltrexone exerts its principal pharmacological effects through blockade of the mu-opioid receptor. Endogenous opioids are involved in modulating the expression of alcohol's reinforcing effects. Mice that lack the mu-opioid receptor do not self-administer alcohol. Naltrexone also modifies the hypothalamic-pituitary-adrenal axis to suppress ethanol consumption.

The usual dose of naltrexone is 50 mg/day, but some trials have used up to 100 mg/day.

Efficacy — Multiple metaanalysis of clinical trials for alcohol dependence found naltrexone to reduce alcohol consumption compared with placebo. As an example, a 2010 meta-analysis of 50 randomized trials with 7793 alcohol dependent participants found that naltrexone reduced the risk of heavy drinking to 83 percent of the risk in the placebo group (relative risk [RR] 0.83, 95% CI 0.76-0.90) and decreased drinking days by about 4 percent.

Naltrexone may be particularly efficacious in individuals with genetic susceptibility. Preliminary evidence suggests that individuals with the Asp variant of the OPRM1 gene are less likely to experience relapse when receiving naltrexone, but further study is needed to confirm the finding. Patients who were heterozygous for the Asp-40 allele were almost six times more likely to have a favorable outcome with naltrexone treatment than those who did not carry this allele.

Adverse effects — Common side effects of oral naltrexone are nausea, headache, and dizziness, which subside with continued use. Fivefold elevation in liver enzymes occurred in 11 of 614 patients who received naltrexone in the COMBINE Study. Enzyme levels returned to baseline after discontinuation of medication in the nine patients who had stopped drinking and

returned for follow-up. Liver enzymes should be monitored periodically during naltrexone treatment.

Depot naltrexone — Depot preparations of naltrexone may improve adherence by reducing the frequency of medication administration from daily to monthly and by achieving a steady therapeutic level of medication, thus avoiding peak effects that can exacerbate adverse events. There are three extended-release, injectable formulations of naltrexone (Vivitrol, Naltrel, and Depotrex). There are no published head-to-head comparisons of their efficacy or bioavailability.

Only Vivitrol has been approved for use in the US, at a dose of 380 mg every four weeks. The injectable suspension should be administered via intramuscular injection to the gluteal area using the provided 1.5 inch 20-gauge needle. The US Food and Drug Administration has warned against other forms of administration including IV or injection subcutaneously or into fatty tissue on the basis of post-marketing reports of serious injection site reactions (See 'Adverse effects' above.).

Efficacy — A large randomized trial found subjects receiving Vivitrol 380 mg monthly had a 25 percent greater reduction in the rate of heavy drinking after 24 weeks compared with those receiving placebo (HR 0.75, 95% CI 0.60-0.94). While subgroup analysis suggested that the treatment may be less effective in women, the proportion of women in this study was relatively small, and these findings may be due to patient characteristics that differed between men and women.

A multi-site randomized trial of the Naltrel formulation did not show a significant difference in the primary outcome, time to first heavy-drinking day, compared with placebo (median of 11 versus 6 days). However, Naltrel was more efficacious than placebo at increasing the mean number of abstinent days (53 versus 46 days).

Adverse effects — Common adverse events observed among subjects receiving Vivitrol included nausea (33 percent), fatigue (20 percent), and decreased appetite (13 percent). Serious adverse events were reported for two trial participants receiving naltrexone who experienced an interstitial pneumonia and an allergic-type eosinophilic pneumonia, both of which resolved with treatment.

In 2008, the Food and Drug Administration (FDA) in the United States (US) reported 196 cases of serious injection site reactions from post-marketing surveillance including induration, cellulitis, hematoma, abscess, and necrosis. The FDA advised that patients be told to report injection-site pain, swelling, bruising, pruritus, or redness that does not improve within two weeks, and that a surgical consult be considered for worsening reactions.

Acamprosate — Acamprosate's principal anti-drinking neurochemical effect has been attributed to the modulation of glutamate neurotransmission at metabotropic-5 glutamate receptors.

The usual dose for acamprosate is 666 mg three times daily. Lower doses should be considered for some patients, including those with renal impairment, body weight less than 60 kg, or a history of response to a lower dose.

Efficacy — Multiple metaanalysis have found acamprosate to reduce alcohol consumption compared with placebo in patients with alcohol dependence. As an example, a meta-analysis of 24 randomized trials of 6915 participants compared treatment with acamprosate to placebo or active control. Acamprosate reduced the rate of patients returning to any drinking (relative risk [RR] 0.86, 95% CI 0.81-0.91; NNT = 9) and increased the cumulative abstinence duration by an average of 11 percent. Acamprosate was found not to have a significant effect on heavy drinking.

The evidence on the efficacy of acamprosate has evolved over time and requires further investigation. A 2004 meta-analysis of the 17 European trials found that acamprosate increased six-month abstinence rates compared with placebo (36.1 versus 23.4 percent). Positive results were primarily seen for maintenance of abstinence rather than reduction of drinking by non-abstinent patients.

Three subsequent trials conducted in the US and Australia found acamprosate did not improve primary outcomes, including percentage of alcohol-free days and time to first heavy drinking. One of the trials, the COMBINE Study, found acamprosate (either alone or in conjunction with a psychosocial intervention) to be no more effective than placebo, while naltrexone was significantly more effective than placebo, indicating that the trial was adequately designed and powered to detect significant effects. (See 'Oral naltrexone' above.)

It is not known whether discrepant findings between the European and US trials result from differences in sample composition, study methodology, or other factors. As examples of sample differences, the European trials on average enrolled subjects with more severe alcohol dependence treated in less controlled environments. The COMBINE study, conducted in the US, limited enrollment to individuals with at least four days of abstinence and no more than 21 days, while the European trials tended to enroll individuals abstinent for longer periods.

Adverse effects — Acamprosate is generally well tolerated at doses of up to 3 g/day. The most prominent adverse events are diarrhea, nervousness, and fatigue, which usually subside with continued use. Because acamprosate is excreted mostly unchanged by the kidneys, rather than the liver, it can be used safely in severely alcohol-dependent individuals with liver disease. Acamprosate dosage needs adjustment for renal insufficiency and is contraindicated in patients with renal failure.

SECOND-LINE MEDICATIONS

Disulfiram — Disulfiram is an aversive agent that does not directly influence motivation to drink, but discourages drinking by causing an unpleasant physiologic reaction when alcohol is consumed. Clinical trials suggest that disulfiram is effective principally when taken routinely under supervised conditions.

Disulfiram inhibits aldehyde dehydrogenase and prevents the metabolism of alcohol's primary metabolite, acetaldehyde. Drinking alcohol while taking disulfiram results in the accumulation of acetaldehyde in the blood, which causes unpleasant effects such as sweating, headache, dyspnea, lowered blood pressure, flushing, sympathetic overactivity, palpitations, nausea, and vomiting.

Contraindications — Contraindications to disulfiram include severe myocardial disease and/or coronary occlusion, psychosis, or known hypersensitivity to the medication or other thiuram derivatives. Disulfiram is generally avoided in pregnant and nursing women. (See 'Treatment during pregnancy' below.)

Administration — Disulfiram is initially dosed at 500 mg/day for one to two weeks, followed by an average maintenance dose of 250 mg/day with a range from 125 to 500 mg based on the severity of adverse effects. The medication should not be used by patients with current alcohol intoxication. Patient education should address "hidden" forms of ethanol (eg, tonics and mouthwashes) and the duration of the drug's activity (up to 14 days after stopping).

Efficacy — A 2014 meta-analysis of two clinical trials with a total of 492 patients did not find a significant difference between disulfiram and placebo in return to any drinking or other primary substance use disorder (SUD) outcomes. A systematic review found mixed results in one large trial and three smaller trials of disulfiram versus placebo for alcohol dependence. The large study, a 52-week, multi-site trial of 605 US veterans, found disulfiram to be no more effective than placebo in maintaining abstinence or in time to first drink, but it may have reduced drinking days in a subgroup that drank during the study. A high rate of noncompliance with medication was seen.

A subsequent study suggested that disulfiram is effective when the medication is taken routinely under supervised conditions. In a trial, 243 patients with alcohol dependence were randomly assigned to receive disulfiram, naltrexone, or acamprosate with regular supervision over a 12-week period. Compared with patients taking naltrexone or acamprosate, patients taking disulfiram experienced a greater reduction in heavy drinking days and average weekly consumption, and a longer time to first drink. The relative benefits of disulfiram were less prominent in a subsequent, unsupervised treatment period of up to 52 weeks.

Adverse effects — Side effects of disulfiram are usually minor, including fatigue, mild drowsiness, headache, and dermatitis. Severe adverse reactions are rare, but include psychosis and hepatitis. Patients receiving disulfiram should be monitored for hepatotoxicity.

Topiramate — Topiramate, a sulfamate-substituted fructopyranose derivative, has been found to decrease alcohol use in individuals with alcohol dependence. It has not been approved by the US FDA for this indication. Topiramate has two principal mechanisms of action that may contribute to its anti-drinking effects:

- Antagonizing alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors and kainate glutamate receptors.
- Facilitating inhibitory GABA(A)-mediated currents at non-benzodiazepine sites on the GABA(A) receptor.

Topiramate should be titrated up gradually over several weeks to minimize side effects. It is generally initiated at 50 mg/day and increased to a maximum dose of 150 mg twice daily.

A 2014 metaanalysis of three clinical trials with a total of 691 patients with alcohol dependence found topiramate to result decreased consumption compared with placebo on some primary SUD outcomes. Four placebo-controlled trials have shown topiramate to decrease alcohol use among alcohol dependent individuals. As an example, a multi-site trial found that topiramate reduced the percentage of heavy drinking days compared to placebo (43.8 versus 51.8 percent) among 371 men and women with alcohol dependence over 14 weeks. Topiramate was more effective than placebo in percent days abstinent, number of drinks per day, and plasma gamma glutamyl transferase, a biological marker of alcohol intake. Trial dropout rates were higher in the topiramate group compared with placebo (39 versus 23 percent).

Three randomized trials comparing naltrexone to topiramate in patients with alcohol dependence found little difference between the drugs in primary outcomes.

Adverse effects — Adverse effects associated with topiramate include cognitive impairment (eg, word-naming difficulties), paresthesias, weight loss, headache, fatigue, dizziness, and depression. Adverse effects of topiramate are discussed in more detail separately. (See 'Treatment during pregnancy' below and "Antiseizure drugs: Mechanism of action, pharmacology, and adverse effects", section on 'Topiramate'.)

Gabapentin — Clinical trials support the efficacy of gabapentin in treatment for DSM-IV alcohol dependence, though this has not been definitively established in a sufficiently large sample, and there is some concern about its abuse potential. As an example, a trial randomly assigned 150 adult patients with DSM-IV alcohol dependence to treatment with either 900 or 1800 mg/day of gabapentin or to placebo. All patients received concurrent manual-based

counseling. After 12 weeks, abstinence rates were higher in patients receiving gabapentin compared to patients receiving placebo (11 and 17 percent in the 900 and 1800 mg/day groups versus 4 percent in the placebo group, though confidence intervals for pair-wise results overlapped with placebo). Similar overall and pair-wise results were observed for rates of no heavy drinking. There were no serious adverse drug events.

Earlier clinical trials found evidence that gabapentin reduced alcohol consumption in patients with DSM-IV alcohol dependence, but these trials had small sample sizes and other methodologic limitations.

Gabapentin is well tolerated at low and moderate doses; sedation and dizziness can occur at higher doses. In our clinical experience and in published reports, gabapentin is subject to abuse by some patients treated for a SUD.

Baclofen — Clinical trials comparing baclofen (30 mg/day) with placebo in the treatment of alcohol dependence have found mixed results. Two trials with a total of 123 patients found that baclofen led to higher rates of abstinence compared with placebo, while a third trial with 80 patients found no significant differences in abstinence rates or in other primary outcomes compared with placebo:

- A 12-week trial randomly assigned 80 subjects with alcohol dependence to receive baclofen (30 mg/day) or placebo; both groups received a low-intensity psychosocial intervention. No differences were seen in heavy drinking days, days abstinent, or time to relapse.
- A 12-week trial compared baclofen (10 mg three times daily) with placebo in 84 individuals with alcohol dependence and liver cirrhosis. Individuals receiving baclofen were more likely to achieve and maintain abstinence compared with placebo (71 versus 29 percent; OR = 6.3, 95% CI 2.4-16.1). The cumulative duration of abstinence was also greater with baclofen (63 versus 31 days).
- A four-week trial comparing baclofen (30 mg/day) with placebo in 39 subjects with alcohol dependence found greater abstinence rates with baclofen compared with placebo (70 versus 21 percent).

Preliminary evidence from a retrospective case series and a secondary analysis of clinical-trial data suggested that a higher dose of baclofen (60 mg/day) may be effective in alcohol dependence, but this requires further study in randomized trials.

Baclofen treatment was well tolerated in these trials, with no abuse liability. No serious adverse effects were seen, including hepatotoxicity, encephalopathy, or hyperammonemia. Mild-to-moderate side effects occurring at a greater rate than in the placebo group included nausea, vertigo, transient sleepiness, and abdominal pain.

Nalmefene — Nalmefene, an opioid antagonist, has been found to reduce drinking in patients with alcohol dependence using a targeted dosing strategy. Nalmefene has several potential advantages over naltrexone, including absence of dose-dependent liver toxicity, longer-acting effects, and more effective binding to central opiate receptors. Nalmefene is not available in some countries, including the US.

A 2014 metaanalysis of three clinical trials with a total of 608 patients with alcohol dependence found nalmefene to be superior to placebo on some primary SUD outcomes. The three trials used a targeted dosing strategy (ie, taken as needed prior to encountering a high-risk situation). As an example, a trial compared nalmefene using a targeted dosing strategy with placebo in 403 patients. Subjects were instructed to take 10 to 40 mg on days when drinking seemed imminent. After 28 weeks, the mean number of heavy drinking days showed a greater reduction among individuals receiving nalmefene compared with placebo (44 versus 32 percent). Two of the trials used an 18-mg dose of nalmefene.

Mixed results have been found in trials of patients with alcohol dependence comparing daily oral nalmefene with placebo on the primary outcomes of relapse rates and heavy drinking days.

- Two 12-week trials in a total of 126 patients with alcohol dependence compared nalmefene 10 mg twice daily, 40 mg twice daily, and placebo. A meta-analysis of the trials found nalmefene led to a greater reduction in relapse rate compared with placebo (relative risk [RR] 0.62, 95% CI 0.41-0.93). Outcomes did not differ by medication dose.
- A trial of 270 subjects with alcohol dependence compared patients treated with one of three doses of nalmefene (5, 20, or 40 mg) or placebo. No differences in outcomes were found among any of the groups.

Adverse events occurring more commonly with nalmefene than placebo in this trial included nausea, insomnia, fatigue, dizziness, and malaise. In addition, fifteen subjects receiving nalmefene experienced psychosis or dissociation. Adverse events led to discontinuation of nalmefene among 16 percent of subjects and dose reduction among 31 percent.

Selective serotonin reuptake inhibitors — A meta-analysis of seven trials found that selective serotonin reuptake inhibitors (SSRIs) do not effectively treat alcohol dependence in patients who do not have a comorbid mental disorder. These trials have several limitations: short time frames, a preponderance of male subjects, and use of non-standardized psychosocial interventions.

Studies suggest that SSRIs may be effective in more homogenous subgroups:

- A meta-analysis found that SSRIs and other antidepressants can reduce intake when alcohol dependence and depression co-occur. (See "Co-occurring schizophrenia and substance use

disorder: Epidemiology, pathogenesis, clinical manifestations, course, assessment and diagnosis".)

- Preliminary evidence suggests that subtypes of alcohol dependence may respond differently to serotonergic drugs, with more favorable outcomes seen in the group characterized by a later age of onset, a preponderance of psychosocial morbidity, and low familial loading. Lesser response to these agents, or even increased alcohol consumption, has been observed among individuals with an earlier-onset subtype, which has high familial loading and a range of impulsive or antisocial traits suggesting careful assessment and follow-up when using SSRIs in alcohol-dependent individuals.

(See "Serotonin-norepinephrine reuptake inhibitors (SNRIs): Pharmacology, administration, and side effects".)

Ondansetron — Early-onset alcohol dependence (onset of problem drinking prior to age 25 years) differs from late-onset alcohol dependence (onset of problem drinking later than age 25 years) by having associations with greater serotonergic abnormality and antisocial behaviors. Ondansetron, a serotonin 5-HT₃ receptor antagonist used to treat chemotherapy-induced nausea, does not appear to effectively treat all patients with alcohol dependence, but clinical trials suggest that the drug is selectively effective in two clinical subgroups:

- Patients with early-onset subtype of alcohol dependence
- Patients with a specific genetic variant of the serotonin transporter (5-HTT) gene. (See 'Neurobiology' above.)

Clinical trials of ondansetron in samples of patients with alcohol dependence (undifferentiated, early/late, and varied genotypes, respectively) are described below:

- A six-week randomized trial of 71 men with nonsevere alcohol dependence (not differentiated by subtype) found no significant difference between ondansetron and placebo in alcohol consumptions.
- A 12-week randomized trial of 271 individuals with alcohol dependence, which differentiated subjects by age of onset of alcohol dependence, found that ondansetron was more effective than placebo on multiple measures of alcohol intake for those with early-onset of the disorder, but not late-onset. No severe adverse events occurred in the trial; no difference was seen between the ondansetron and placebo groups in rates of mild-to-moderate adverse events.
- A 12-week randomized trial compared ondansetron (4 mcg/kg intravenously injected twice daily) with placebo in 283 individuals classified into one of three categories by genotype: the LL, LS, and SS genotypes in the promoter region of the serotonin transporter (5-HTT) gene. Individuals with the LL genotype who received ondansetron had a lower mean number of drinks

per drinking day (−1.62) and a higher percentage of days abstinent (11.27 percent) than those who received placebo. Individuals with both the LL and TT genotypes who received ondansetron reported fewer drinks per drinking day (−2.63) and a higher percentage of days abstinent (16.99 percent).

Adverse effects — Adverse effects associated with ondansetron include diarrhea, headache, and fever. Ondansetron prolongs the QT interval in a dose-dependent manner, and should be avoided in patients with underlying heart conditions, such as congenital long QT syndrome, or taking other medications that lead to QT prolongation.

OTHER MEDICATIONS — Medications currently under study for alcohol use disorder include other anticonvulsants, antipsychotics, dopamine antagonists, CRF antagonists, neuropeptide Y antagonists, varenicline, and the cannabinoid receptor antagonist rimonabant.

COMBINING MEDICATIONS — Combining medications, particularly those with different mechanisms of action, offers the possibility of more effective treatment for patients who do not respond adequately to an individual agent.

Two trials compared the combination of oral naltrexone and acamprosate, finding mixed results. In a trial of 160 individuals with alcohol use disorder, the group receiving naltrexone and acamprosate experienced fewer relapses and a longer time to first drink than those receiving acamprosate alone. However, the combined medications were no more effective than naltrexone alone. The COMBINE Study did not find an advantage to combined naltrexone-acamprosate treatment compared with either the individual agents or placebo. (See 'Oral naltrexone' above.)

A small, eight-week trial of the combination of ondansetron and naltrexone for early-onset alcohol use disorder led to reduced drinking and reduced levels of carbohydrate-deficient transferrin (a marker of alcohol use) compared with placebo. Combined treatment was not compared with either drug individually.

Two trials found the combination of naltrexone and sertraline (an SSRI) to be no more effective than naltrexone alone in maintaining abstinence among individuals with alcohol use disorder.

COMPARING MEDICATION WITH PSYCHOSOCIAL TREATMENTS —

There are no clinical trials that directly compare medications to psychosocial interventions in alcohol dependence or alcohol use disorder. (See "Psychosocial treatment of alcohol use disorder".)

COMBINING MEDICATION WITH PSYCHOSOCIAL TREATMENTS —

The evidence is mixed as to whether combining medication with a structured psychosocial intervention leads to better outcomes for alcohol use disorder than medication alone (see 'First-

line medications' above and 'Acamprosate' above and "Psychosocial treatment of alcohol use disorder"):

- The COMBINE Study compared naltrexone, acamprosate, a psychosocial intervention, combination naltrexone-psychosocial treatment, acamprosate-psychosocial treatment, and placebo in 1383 patients with alcohol use disorder. The psychosocial intervention integrated aspects of cognitive-behavioral therapy (CBT), 12-step programs, motivational interviewing, and support system involvement. No differences were seen with either medication combined with psychosocial treatment compared with the respective medication alone or the psychosocial treatment alone.
- An earlier, smaller study provided limited evidence suggesting combined naltrexone and CBT were more effective than naltrexone alone.

TREATMENT SELECTION — Limited data are available on comparative effectiveness, drug characteristics, treatment goals, and predictors of response that can inform clinicians' selection among treatments for alcohol use disorder. The suggestions that follow are based on these data and our clinical experience.

- We suggest that patients with moderate to severe alcohol use disorder initially be offered a choice of medication or an evidence-based psychosocial intervention such as cognitive behavioral therapy (CBT). There are no trials comparing the two, and findings are mixed as to whether the combination of both is more effective than either intervention alone. (See 'Comparing medication with psychosocial treatments' above and 'Combining medication with psychosocial treatments' above.)
- Patients with the mild subtype of alcohol use disorder who are currently drinking heavily and risk serious consequences can be considered for these treatments on a case-by-case basis. Data on the efficacy of these interventions are typically not generalizable to patients with the mild subtype.
- For patients who do not achieve remission or an adequate reduction in heavy drinking with medication or a psychosocial intervention, we recommend combining modalities if the first was partially effective or switching modalities if the first was ineffective. (See 'Combining medication with psychosocial treatments' above.)
- When medication is used for alcohol use disorder, we suggest first-line treatment with naltrexone for most patients over other medications. Metaanalyses of trials comparing acamprosate with naltrexone found no significant difference between them for return to any drinking or return to heavy drinking. An earlier, 2006 meta-analysis concluded that acamprosate may be more effective for maintenance of abstinence (compared with placebo, relative risk [RR] 0.84, 95% CI 0.78-0.91), while naltrexone was more effective for reduction of

heavy drinking (compared with placebo, relative risk [RR] 0.80, 95% 0.71-0.91). (See 'Acamprosate' above and 'First-line medications' above.)

Predictors of therapeutic response to naltrexone include family history of alcohol use disorder and strong cravings for alcohol. (See 'First-line medications' above.)

Predictors of therapeutic response to acamprosate include increased levels of anxiety, physiological dependence (ie, severe symptoms of withdrawal), negative family history, late age of onset, and female gender. (See 'Acamprosate' above.)

Depot naltrexone is an option for treatment of patients likely to be nonadherent to daily oral medication. Nonadherence presents an impediment to effective pharmacotherapy for a substantial proportion of patients with alcohol use disorder in clinical trials and in practice. As an example, 37 percent of patients taking naltrexone in a meta-analysis of clinical trials prematurely discontinued the medication during the study. (See 'Depot naltrexone' above.)

- For pharmacotherapy of an alcohol use disorder in patients with acute hepatitis, liver enzymes greater than three to five times normal, or liver failure, we suggest acamprosate over other medications. Baclofen would be a reasonable alternative. Naltrexone has been associated with hepatotoxicity, particularly at high doses, and acamprosate has been shown to be safe for patients with alcohol use disorder and severe liver disease. Baclofen appears safe and effective for patients with alcohol use disorder and cirrhosis. (See 'First-line medications' above and 'Acamprosate' above and 'Baclofen' above.)

- Acamprosate should also be considered as an alternative to naltrexone for patients under concurrent treatment with opioids. (See 'Acamprosate' above.)

- Acamprosate is not indicated for the induction of abstinence in actively drinking patients. (See 'Acamprosate' above.)

- For patients with alcohol use disorder for which naltrexone and acamprosate are ineffective or not indicated, other options with evidence supporting efficacy include disulfiram, topiramate, gabapentin, baclofen, and ondansetron.

- Disulfiram should not be used unless the treatment goal is to maintain abstinence. Because this medication is associated with particularly high rates of nonadherence, use should be limited to highly motivated patients and those who take medication under supervision. (See 'Disulfiram' above.)

- Serotonergic agents may be more effective when used selectively for subtypes of alcohol use disorder. Preliminary evidence suggests that SSRIs may be more effective for a late-onset subtype and comorbid depression. Ondansetron, a serotonin antagonist, may be more effective for patients with an early-onset disorder and for patients with a specific genetic variant of the

serotonin transporter (5-HTT) gene. (See 'Selective serotonin reuptake inhibitors' above and 'Ondansetron' above.)

TREATMENT DURING PREGNANCY — There is a paucity of data on the safety of pharmacologic therapies for alcohol use disorder in pregnant women. In weighing risks and benefits of prospective treatment, one should also consider the harmful effects of alcohol to the mother and to the developing fetus. (See "Alcohol intake and pregnancy".)

If feasible, treatment of pregnant women with substance abuse disorders should be managed by clinicians with specialized expertise in this area. Potential issues with medications used for alcohol use disorder include the following:

- Naltrexone is used in pregnancy more commonly than are other medications for alcohol use disorder because of the absence of known, harmful effects; this decision should be made cautiously due to the absence of well-controlled studies of any of the medications in humans.
- Disulfiram may harm the developing fetus by increasing levels of acetaldehyde. In addition, the physiologic reaction between disulfiram and ethanol in the mother presents a potential risk to the fetus. For these reasons, disulfiram is rarely used in pregnancy.
- Opiate antagonists such as naltrexone are used with caution in pregnancy due to their potential to induce a withdrawal syndrome, harmful to the fetus, among patients surreptitiously taking opiates.
- Acamprosate is teratogenic in animal studies. There are no adequate studies of pregnant women with fetal exposure.
- There is an increased risk for the development of cleft lip and/or cleft palate (oral clefts) in infants born to women treated with topiramate during pregnancy, but this occurrence is rare.
- Topiramate has been found to be teratogenic in animal studies. It crosses the placenta in humans. A preliminary report on 203 prospectively followed pregnancies exposed to topiramate found a high rate of major congenital malformations. (See "Risks associated with epilepsy and pregnancy".)

(See "Substance misuse in pregnant women" and "Alcohol intake and pregnancy" and "Management of moderate and severe alcohol withdrawal syndromes".)

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics

patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Basics topics (see "Patient education: Alcohol use — when is drinking a problem? (The Basics)")
- Beyond the Basics topics (see "Patient education: Alcohol use — when is drinking a problem? (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- Medications to treat alcohol use disorder are needed despite the availability of effective psychosocial interventions. As many as 70 percent of individuals relapse after psychosocial treatment alone. (See 'Introduction' above.)
- Pharmacologic treatment of alcohol abuse use disorder has mostly focused on altering the reinforcing effects of alcohol use. Many available or promising medications appear to act by modulating the function of opioids, glutamate (with or without GABA), or serotonin. (See 'Neurobiology' above.)
- Goals for treatment include abstinence, the traditional objective of alcohol treatment, or reduction of heavy drinking, a measure of alcohol intake strongly related to negative life consequences. (See 'Treatment principles and overview' above.)
- We suggest that patients with moderate to severe alcohol use disorder initially be offered a choice of medication or an evidence-based psychosocial intervention, or both (**Grade 2C**). Patients with the mild subtype, current heavy drinking, and risk of serious consequences can be considered for medication treatment on a case-by-case basis. All patients should receive some psychosocial treatment. (See 'Indications' above and "Psychosocial treatment of alcohol use disorder" and 'Treatment selection' above.)

Patients who do not achieve remission or an adequate reduction in heavy drinking should receive a trial of the other modality or a combination of modalities. (See 'Treatment selection' above and 'Combining medication with psychosocial treatments' above.)

- For patients taking medication, we suggest naltrexone for most patients with alcohol use disorder over other medications (**Grade 2B**). Depot naltrexone should be used when there is a significant risk of nonadherence with daily administration; patients should be monitored for

injection site reactions. Naltrexone is not appropriate for patients with liver disease or who are taking opioids. (See 'First-line medications'above.)

- For pharmacotherapy of an alcohol use disorder in patients with acute hepatitis, liver enzymes greater than three to five times normal, or liver failure, we suggestacamprosate over other medications (**Grade 2C**). Baclofen would be a reasonable alternative. The evidence for the efficacy ofacamprosate is mixed. Its use may be considered for individuals with liver disease or those who do not respond to other medications. (See 'Acamprosate' above.)

- For patients with alcohol use disorder for which naltrexone andacamprosate are ineffective or not indicated, other options with evidence supporting efficacy include disulfiram, topiramate, gabapentin, baclofen, and ondansetron. (See 'Second-line medications' above.)

- Use of disulfiram should be reserved for individuals who are highly motivated to maintain abstinence, and are either treatment adherent or take the medication in a supervised setting. (See 'Disulfiram' above.)

- In treating alcohol use disorder with topiramate, care must be taken to increase the dose slowly to avoid adverse events including cognitive impairment (eg, word-naming difficulties), paresthesias, and weight loss. (See 'Topiramate'above.)

- Clinical trials of baclofen in alcohol use disorder have led to mixed results. Larger randomized trials are needed to determine its efficacy. (See 'Baclofen'above.)

- Targeted dosing of nalmefene has been found to improve outcomes in alcohol use disorder in clinical trials; trials of daily dosing have led to mixed results. (See 'Nalmefene' above.)

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MESSAGE FOR PSYCHIATRISTS

Karachi Psychiatric Hospital was established in 1970 in Karachi. It is not only a hospital but an institute which promotes awareness about mental disorders in patients as well as in the general public. Nowadays it has several branches in Nazimabad, North Nazimabad, and in Quaidabad. In addition to this there is a separate hospital for addiction by the name of *Karachi Addiction Hospital*.

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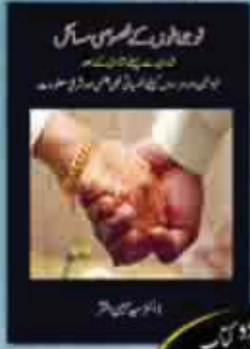
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Sex Education for Muslims

The Quran and Hadees provide guidance in all affairs of life. It is imperative for a Muslim to study the Quran and Hadees, understand them, and make these principles a part of daily life. The most important human relationship is that of marriage. It is through this institution that the procreation and training of the human race comes about. So it is no wonder that the Quran and Hadees give us important guidance on this matter. But it is unfortunate that our authors, teachers and imams avoid this topic in their discourses due to a false sense of embarrassment. Moreover most of them are not well versed in the field of medicine and psychology. Therefore it's only people who have knowledge of both religion as well as medicine who should come forward to speak and write on the subject. We have included in this book all passages referring to sexual matters from the Quran, Hadees and Fiqh. These passages provide guidance to married as well as unmarried youngsters. If one reads this matter it would be easier to maintain proper physical and sexual health, along with an enjoyable marital life. The reading of this matter as well as using it in one's life will be considered equal to.

The same book has been translated into Urdu under the title of
"جنسی مسائل کے خصوصی مسائل"

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Author: **Dr. Syed Mubin Akhter** (M.B.B.S)

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Index of Topics

Bulletin January to September 2018

A

AD Patients

11.

Addiction

144.

Adolescent

295, 309.

Adult Separation Anxiety

14.

Agoraphobia

14.

Alcohol

278, 332.

Alzheimer's Disease

135.

American

204.

Anorexia Nervosa

278, 305.

Antidepressants

24, 202, 268, 303, 308.

Antipsychotic

178.

Anxiety

112, 239.

Anxiolytic

303.

Arterial Dissection

50.

Augmentation

178.

Autism

201.

Autoimmune Epilepsy

77.

Autoantibodies

53.

B

Bad Behaviors

277.

Benzodiazepine

200.

Bias

54.

Benzodiazepine

200.

Bias

54.

Bipolar Illness

52.

Bipolar Disorder

110, 295.

Brains

66.

C

Catatonia

321.

Celiac Disease

9, 305.

Childhood

92.

Children

309.

Circadian Rhythms

13.

Coffee

118.

Cognition

279.

Cognitive Behavioral Group

Therapy

174, 202.

Contraceptives

270.

Conversion Disorders

1.

Cooking

97.

Corticosteroids

292.

Climate Change

64, 66.

Clozapine

86.

D**Death Rate**

244.

Dementia

246, 301, 308.

Delirium

321.

Dependence

200.

Depression27, 49, 54, 61, 98, 112, 133,
203, 207, 209, 267, 306.**Depressive**

81, 119.

Deprivation

183.

Diabetes

117.

Diet

61, 207

Diet Drinks

306.301

Doctors

327.

E**Early Drinking**

279.

Endo-Brain

7.

Epilepsy

119.

Exercise

98.

Extinction

15.

F**Factitious Disorder**

122.

Fertility Hormone

8.

Fear Extinction

275.

First Episode Psychosis

244.

G**Genital HPV**

204.

Geriatric Psychiatry

101.

Gluten

9.

H**Heart**

66.

Hormones

269.

Hypothyroidism

310.

I**Insomnia**

12.

IUD

22.

K**Ketamine**

34, 37, 40, 44.

Kidney Disease

48, 274.

L**Letter**

282.

Lithium

274.

Low Plasma Drug Level

272.

Lungs

66.

M**Macula**

80.

Major Depressive Disorder

202.

Marriage

327.

Medical Catatonia

321.

Menopausal Symptoms

249.

Microbiota-Gut-Brain Axis

303.

Migraine

239.

Mild Cognitive Impairment

273, 294.

Mood Scale

137.

Monotherapy

178.

Mortality

200.

N**Neurofeedback**

306.

Neuropathy

109.

Nodding Syndrome

77.

Non-Epileptic Seizures

311.

Nurturance

183.

Nutrition

84.

O**Obstructive Sleep Apnea**

55.

Off Label

268.

Oral Corticosteroids

292.

Overweight

200.

Oxytocin

15, 16.

P**Pain**

49, 239.

Panic

14.

Pharmacotherapy

332.

Polysomnography

55.

Post-Traumatic Stress Disorder

91, 182, 184.

PPIS

48.

Predict

203.

Predictors

203.

Pregnancy

181.

Primary Care

304.

Preuptial

327.

Probiotics

303.

Psychogenic Non-Epileptic Seizures

311.

Psychosis

19, 226.

Psychotherapy

52.

Psychosexual

201.

PTSD

56.

R**Remission**

203.

Relapse

226.

Retinal Detachment

80.

Rural Children

185.

S**Schizophrenia**

178, 228, 272

School
 295.
Screening
 209.
Self care
 197.
Serotonin Receptor
 51.
Sertraline
 281.
Sex
 95.
Sexual Harassment
 20.
Seizure Disorders
 53.
Smart Phone App
 184.
Social Anxiety Disorder
 174.
Social Interactions
 16.
Somatic Disorders
 122.
SSRIS
 273.
Stigma
 67.
Stress
 270, 303.
Stroke
 301.
Suicide
 238, 269, 309.
Substance Induced Psychosis
 280.
Super Agers
 293.
Surgery
 78.

T
Tardive Dyskinesia
 108.
Tea
 118.
Teenagers
 278.

Temperament
 16.
Testosterone Therapy
 116.
Tobacco
 17.
Transgender
 32.
Trancelike
 205.
Treatment
 171, 267.
Trials
 54.

U
United States
 238.
Urdu
 138, 188, 189, 190, 287.
USA
 172.

V
Violence
 172, 295, 307.

W
Weight
 181.
Well-body
 133.

Y
Yogurt
 81, 119.
Young People
 277.
Youth
 98, 244, 279.

Z
Zinc
 27.