Focus
The Journal of Lifelong Learning in Psychiatry

Focus (Am Psychiatr Publ). Spring 2019; 17(2): 88–97.
Published online 2019 Apr 10. doi: 10.1176/appi.focus.20180042: 10.1176/appi.focus.20180042
PMCID: PMC6526999
PMID: 31975963

Treatment for Substance Use Disorder With Co-Occurring Mental Illness

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Substance use disorders are overrepresented among individuals with mental illness, and diagnosis and treatment of co-occurring disorders can be challenging. This review describes the epidemiology and treatment of co-occurring disorders, with a focus on major depressive disorder, anxiety disorders, and ADHD.

Keywords: Dual diagnosis, Depression, ADHD, Alcohol use disorder, Anxiety disorders

Abstract

Substance use disorder is a highly prevalent condition, leading to significant morbidity, mortality, and burden on the health care system. Substance use disorders are overrepresented among individuals with a mental illness. The term "dual diagnosis" was introduced by the World Health Organization in the mid-1990s and refers to the co-occurrence of a substance use disorder with mental illness—a more recently used term is "co-occurring disorders." In the past decade, substantial progress has been made toward expanding psychotherapeutic and pharmacotherapeutic treatments for treating co-occurring disorders. Yet management remains a challenge among clinicians and has been a source of confusion and considerable controversy. This review describes the epidemiology and treatment of co-occurring disorders, with a focus on major depressive disorder, anxiety disorders, and attention-deficit hyperactivity disorder. Substance use may make diagnosis of the underlying psychiatric condition difficult, and a period of abstinence may be necessary. Findings from efficacy studies of medications used to treat co-occurring disorders are reviewed, as are results of preliminary studies of newer treatments, such as topiramate, ketamine, noninvasive brain stimulation, and deep brain stimulation. Treatment recommendations that combine medications and psychosocial interventions are summarized.

Keywords: Dual diagnosis, Depression, ADHD, Alcohol use disorder, Anxiety disorders

According to a 2017 report published by the Substance Abuse and Mental Health Services Administration, there were 4.9 million new users of alcohol, three million new users of marijuana, two million new misusers of prescription pain medications, and 1.9 million new users of cigarettes among persons ages 12 and over (1). Moreover, in 2017 19.7 million Americans ages 12 and over had a diagnosable substance use disorder—14.5 million with an alcohol use disorder and 7.5 million with a disorder involving an illicit drug (1). This figure represents 6.0% of all individuals ages 12 and over in the United States.

Given that the base rate of prevalence of substance use disorders is 6% and that individuals with a substance use disorder account for nearly 20% of all those with a mental illness, clearly, substance use disorders are overrepresented among individuals with a mental illness. For clinicians this presents a formidable challenge because their patients' underlying psychiatric disorders may worsen a comorbid substance use disorder, and similarly, a substance use disorder may exacerbate an existing psychiatric disorder. Therefore, clinicians need to be aware of the impact that these conditions have on one another and how co-occurring mental and substance use disorders affect the treatment and prognostic outcomes of their patients. For the purposes of this review, we focus on the comorbidity of and therapeutic recommendations for substance use disorder in relation to major depressive disorder, anxiety disorders, and attention-deficit hyperactivity disorder (ADHD).

Epidemiology of Comorbid Mental and Substance Use Disorders

Depression

Approximately 7% of individuals in the United States report having recently experienced a major depressive episode (1, 2), and according to the Centers for Disease Control and Prevention, 8% of Americans ages 20 and over have experienced depression (3, 4). Previous work has reported strong associations between depression and the presence of a substance use disorder, with odds ratios ranging between 1.3 and 2.6 (5, 6). Epidemiological research has also shown that adolescents with a substance use disorder are more likely than those without one to have major depressive disorder and that adolescents with depression are more likely than those without depression to develop a substance use disorder (7, 8). In 2017, the percentage of adolescents aged 12 to 17 who used illicit drugs in the past year was higher among those with a past year major depressive episode than it was among those without a past year major depressive depressive episode (29.3% versus 14.3%) (1). Also, previous work has demonstrated that outcomes tend to be significantly worse among patients diagnosed as having both major depressive disorder and a substance use disorder, compared with patients who have only one of these diagnoses (9–11). This illustrates the interplay between these conditions and the need for the physician to consider and treat both disorders in tandem.

Anxiety Disorders

The lifetime prevalence of any anxiety disorder is 38% among women and 27% among men (12). The lifetime and 12-month prevalence of generalized anxiety disorder among Americans ages 13 and older are 4.3% and 2%, respectively, with generalized anxiety disorder being more common among women than among men (12). Previous reports of the lifetime prevalence of comorbid generalized anxiety disorder and substance use disorder are 2%, which is equivalent to the lifetime prevalence of generalized anxiety disorder without a substance use disorder (13). A meta-analysis by Lai et al. (5) also found that individuals with lifetime drug dependence were as much as 2.9 times more likely to develop illicit drug use and any anxiety disorder. Of interest, although anxiety disorders are more common among women, men with anxiety disorders appear to be more likely than women with these disorders to have a comorbid substance use disorder (12).

ADHD

The prevalence of ADHD among adults in the United States is 2.5%−4.4%, affecting nearly nine million adults across the country (14). Like depression and anxiety disorders, ADHD is overrepresented among individuals with a substance use disorder, with prevalence estimates ranging from 9.9% to 54% among adults and 8% to 44.3% among adolescents (15). Although various studies assessing the rate of comorbidity have reported highly variable values, a meta-analysis of the available literature estimated that the true prevalence rate of comorbid ADHD and substance use disorder is 23% (15). Recent meta-analyses have also reported that the risk of developing a substance use disorder varies by substance among children diagnosed as having ADHD (16, 17). For example, compared with children without a diagnosis of ADHD, those with an ADHD diagnosis are approximately twice as likely to develop a nicotine or cocaine use disorder, 1.3–2.0 times as likely to develop an alcohol use disorder, and almost three times as likely to develop a cannabis use disorder (16, 17). Estimates of the relative risk of developing any substance use disorder range from 1.47 to 2.64 times the risk for the general population. Of interest, children with ADHD were also more likely to report having ever used marijuana or nicotine, but not alcohol, compared with children without ADHD (16).

Complicating the matter further is the fact that individuals with ADHD often have other comorbid psychiatric disorders in addition to a substance use disorder. For example, among individuals with ADHD, 35%−50% have experienced a depressive episode in their lifetime and as many as 60% of adults diagnosed as having ADHD reported having an anxiety disorder at some point in their lifetime (18).

General Risk of Overdose

Aside from the chronic illnesses associated with long-term substance use, individuals with a substance use disorder also face the acute risk of overdose. An epidemiological study by Bohnert et al. (19) followed 327,631 individuals with a substance use disorder, among whom 2,324 died of an accidental overdose. The study found that among the various substances of abuse, opioid use disorder carried the greatest risk of overdose (19). Depression was also found to be a significant predictor of death due to overdose; 23.6% of all individuals who died of overdose were diagnosed as having some form of a depressive disorder (19). The hazard ratios for alcohol- or illicit drug–related overdoses were 1.89 and 1.23, respectively, for depressive disorders and for anxiety disorders (not including posttraumatic stress disorder [PTSD]) (19). Strikingly, these figures were found to increase to 3.02 and 3.07, respectively, in the case of medication-related accidental overdose (19). Ultimately, accidental overdose alone is insufficient for diagnosing a chronic substance use disorder. However, these findings at the very least indicate that people with certain psychiatric conditions who also use either illicit substances or opioid medications are at an elevated risk of overdose, compared with the general population.

Alcohol use and substance use disorders in general increase an individual's risk of attempted suicide, with comorbid major depression and alcohol use disorder further elevating the risk (20). These findings provide support that underlying psychiatric comorbidities may exacerbate the risk of overdose among individuals with a substance use disorder.

Diagnostic Pitfalls in Co-Occurring Disorders

There are numerous challenges involved in both identifying and treating substance use disorders comorbid with other psychiatric disorders. The relationship between substance use disorder and conditions such as depression, anxiety, and ADHD is a bidirectional one, with the comorbid conditions often affecting treatment outcomes. Co-occurring disorders also have the added effect of obscuring one another, making it difficult to make appropriate diagnoses in this patient population. One reason is that the behaviors seen among patients with depression, anxiety, and ADHD are often mimicked among those with a substance use disorder. For example, acute intoxication from simultaneous alcohol and stimulant use can lead to manic- and hypomanic-like symptoms, and patients in withdrawal often exhibit agitation and mood-based symptoms seen with anxiety or depressive disorders (21). Similarly, chronic use of cocaine and amphetamines may lead to a decrease in appetite, diminished sleep, grandiose thoughts, and paranoid thinking patterns—symptoms that are often seen in cases of bipolar disorder. Alternatively, chronic use of central nervous system depressants, such as alcohol, benzodiazepines, and opioids, may lead to anhedonia, depressed mood, and abnormal sleep patterns (21).

To effectively diagnose an underlying psychiatric disorder, it may be necessary for a patient to be abstinent for weeks, and sometimes months, to allow for the symptoms of both substance use and withdrawal to fully subside. Drugs that act over longer durations require longer abstinence periods than do shorter-acting compounds. Often, getting a careful history of the patient's symptoms that presented during past periods of abstinence is the best available method to rule out whether those symptoms are indicative of a primary psychiatric disorder or a psychiatric disorder that is a consequence of substance use (substance-induced disorder). However,, this may not be possible, and then the temporal relationship of the psychiatric disorder and the substance use disorder needs to be identified to determine whether the psychiatric disorder is a substance-induced disorder. When the onset of the two disorders occurs concurrently, then the clinician may have to use his or her judgment about whether the psychiatric symptoms are more intensive than what would be expected from the substance use disorder and thus require a targeted clinical intervention.

Other methodological approaches can also be applied to guide physicians. Urine toxicology, screening instruments (Addiction Severity Index, Beck Depression Inventory, and the Hamilton Depression Rating Scale), physical examination, substance use history, family history, premorbid history, and consultation with family members or of prior therapists' information can help delineate a patient's history of substance use problems and psychiatric illness.

Treatment Guidelines for Co-occurring Mental and Substance use Disorders

Patients with co-occurring disorders often require an integrated treatment approach—that is, to achieve significant improvements in the patient's condition, physicians must properly utilize both pharmacological and psychotherapeutic approaches.

Pharmacologic and Psychosocial Treatment of Depression and Substance Use Disorder

Depression places a significant burden on individuals with a substance use disorder. Previous research has demonstrated that individuals with persistent depression and other depressive disorders are more likely to have a substance use disorder, compared with the general population (22–27). Evidence strongly suggests that these conditions are associated with neurobiological impairments in the brain. For example, abnormalities in the circuitry of the frontal-limbic region of the brain, particularly the nucleus acumbens, have been implicated in the loss of reward responsiveness, which is believed to play a key role in depression (28). Similar alterations in the reward pathways of the brain are also observed among individuals with a substance use disorder (29). Neuroimaging studies have also shown reduced metabolic activity in the frontal-limbic region, hyperactivity of the amygdala, and a deficiency of dopamine-2 receptors in the brains of cocaine- and alcohol-dependent patients (30). Cocaine use disorder and pathological gambling are also linked to abnormal ventrolateral prefrontal cortex function, further implicating abnormalities in the reward processing system as a contributor to substance use disorder (31).

The current stance on addressing comorbid depression and substance use disorder is to treat the depression in the context of substance use disorder and to tailor treatment for depressive symptoms to the severity with which they present (32). Initiation of antidepressant medication may be indicated for individuals with moderate to severe depressive symptoms, depending on the history of the individual's symptoms, the development of the symptoms during stable substance use, and the presence of suicidal ideation secondary to depression. Meta-analysis indicates that antidepressant medication may be successful in alleviating depressive symptoms, and possibly reducing substance use, among individuals with a substance use disorder and depression (32, 33). The overall effect size of this intervention was found to be small to moderate, and as noted by the authors of these publications, positive outcomes usually require at least 6 weeks of treatment (32, 33).

The current body of evidence includes mixed findings in terms of which antidepressant medication is superior for alleviating the symptoms of depression (34, 35). The most commonly prescribed antidepressants are selective serotonin reuptake inhibitors (SSRIs) (36). However, SSRIs have produced inconsistent results in treating depression among individuals with a substance use disorder (37–41). This may be related to the small samples, short treatment duration, or dosages used in some of these studies. However, SSRIs are still recommended as the first-line medication because of their safety, tolerability, and lower risk of interaction with alcohol or other drugs (42, 43).

If a patient fails to respond to SSRIs, alternative medications include dopaminergic, noradrenergic, or mixed-mechanism-of-action antidepressants, such as bupropion, venlafaxine, mirtazapine, and tricyclic antidepressants (TCAs). Among these, TCAs have the largest quantity of empirical support with regard to efficacy (44–47). In a double-blind placebo trial by Nunes et al. (47), imipramine reduced depressive symptoms to a greater degree than placebo among methadone-maintained opioid users. However, study participants in the imipramine group also experienced more cardiac and pulmonary side effects than those in the placebo condition. Another study, by McGrath et al. (48), found imipramine to be associated with improvement in depression among both adequately treated and intent-to-treat patients. However, 13 patients discontinued the study because of side effects, such as severe sedation, dizziness, constipation, gastrointestinal distress, and urinary retention. These findings demonstrate that although TCAs are effective in reducing the symptoms of depression, their tolerability is unfortunately low. This, along with the high risk of fatal drug interactions and the low therapeutic index, may limit their utility among individuals with comorbid depression and substance use disorder.

The use of psychotherapeutic interventions is also recommended. Interventions such as cognitive-behavioral therapy (CBT), motivational interviewing, 12-step facilitation, and the community reinforcement approach, have been demonstrated to be effective for patients with a substance use disorder (49–54). In the context of a co-occurring substance use disorder and depression, the effect of these approaches in isolation is unfortunately limited.

With regard to alcohol, the greatest outcomes are usually seen with the combination of antidepressants and CBT (41). For example, Cornelius et al. (38) found that the combination of SSRIs and CBT produced greater reductions in drinking and depressive symptoms, compared with CBT alone. Moak et al. (55) reported that the combination of sertraline and CBT produced superior outcomes in terms of alleviating depression and reducing alcohol use, compared with sertraline alone.

In contrast, Schmitz et al. (56) found that among cocaine users, study participants receiving CBT alone had fewer cocaine-positive urine samples than those receiving both CBT and fluoxetine. Daley et al. (57) reported that motivational therapy reduced cocaine use and the severity of depression symptoms, compared with treatment as usual. However, all study participants received antidepressants, which made it impossible to determine whether the motivational therapy would have produced these effects in the absence of antidepressants.

Treatment Recommendations for Co-Occurring Anxiety Disorders and Substance Use Disorder

Anxiety disorders are among the most common class of psychiatric disorders in the United States and across the globe, frequently co-occurring with substance use disorders and causing greater functional impairment, increased disability, and worsening outcomes than for either disorder alone (58–60). Studies among both animals and humans have shown the amygdala and prefrontal cortex to be involved in the development of anxiety and fear (61). The amygdala also constitutes a part of the mesolimbic pathway, which plays a role in the reward response seen in the brain in reaction to substance use (62). Dysfunction in glutamate-mediated neurotransmission from the prefrontal cortex to the nucleus acumbens has been shown to be linked to substance use and compulsive drug seeking (63).

Diagnosing substance use disorder with a co-occurring anxiety disorder can be a challenge, because it is difficult to determine whether a patient's anxiety symptoms are caused by the effects of substance intoxication or withdrawal—that is, one disorder is happening as a direct or indirect consequence of the other—or whether the patient has two independent disorders that co-occur incidentally or because of common risk factors (64, 65). Among all anxiety disorders, generalized anxiety disorder has one of the highest comorbidity rates with substance use disorder, particularly among patients with alcohol use disorder (66). Randomized controlled trials (RCTs) have examined the efficacy of using buspirone in treating anxiety symptoms and alcohol dependence. Results indicated that buspirone performed better in alleviating anxiety and decreasing the frequency and quantity of alcohol consumption among persons with alcohol use disorder and anxiety (67–70). However, the long-term utility of buspirone in reducing anxiety and substance use remains uncertain, and the high placebo response rate makes detecting any possible effects of the treatment difficult. Other medications for treating generalized anxiety disorder, such as paroxetine, sertraline, and escitalopram, have not yet been studied in clinical trials for treating generalized anxiety disorder and comorbid substance use disorder. Benzodiazepines are also effective in treating generalized anxiety disorder, but their use is controversial because of their high abuse liability. Compared with patients with other subtypes of anxiety disorders, patients with social anxiety more often report using alcohol and other drugs to alleviate their symptoms (71). RCTs testing paroxetine demonstrated its efficacy over placebo in treating social anxiety and alcohol use disorder simultaneously (72); however, treatment was often discontinued because of the high rates of sexual dysfunction as a side effect.

Some studies have also suggested using CBT as a form of psychosocial treatment that can help decrease both anxiety symptoms and risk of relapse among patients with comorbid generalized anxiety disorder and substance use disorder (73, 74). A review by Hesse (75) of the available literature indicated that integrated psychotherapeutic approaches are effective in terms of increasing days abstinent and decreasing the symptoms of anxiety. A review by Fatseas et al. (76) found that the combination of CBT and antidepressants produced the greatest outcomes among opioid-dependent individuals with comorbid anxiety (76). These findings underscore the need for physicians treating comorbid anxiety and substance use disorder to implement both pharmacological and psychotherapeutic treatments to maximize the quality of care provided to their patients.

ADHD and Substance Use Disorder Treatment

ADHD is a syndrome that is characterized by a persistent pattern of inattention or impulsivity and hyperactivity that is inappropriate for a given age and developmental level. ADHD is the most prevalent mental disorder in childhood (77, 78), and almost 60% of children with ADHD have ongoing symptoms as adults (79–82). Underactivity of the dopamine reward pathway as evidenced by studies showing decreased dopamine transporter binding across different brain areas, such as the nucleus acumbens, midbrain, left caudate, and hypothalamus (83–85), is implicated in ADHD neuropathology. Similar deficits in dopaminergic activity were demonstrated among individuals with substance use disorders (85, 86), suggesting that both ADHD and substance use disorders may involve abnormalities in circuits related to reward processing (16).

Diagnosing ADHD in the context of substance use disorder is difficult; the risk of underdiagnosis and overdiagnosis is high among patients with a substance use disorder. Clinicians often fail to assess for ADHD, which leads to underdiagnosis. However, overdiagnosis can occur when the symptoms of intoxication or withdrawal are thought to be ADHD symptoms. A practical approach for the diagnosis of ADHD among adults with a substance use disorder might be to consider whether ADHD symptoms began during early adolescence, whether symptoms were noted on school performance reports, and whether symptoms occurred during periods of abstinence. Also, collateral information from the family about whether the individual showed ADHD symptoms in childhood or adolescence, prior to the onset of substance use, can be helpful (78). In the absence of this information and when symptoms present after a substance use disorder, a diagnosis of ADHD is less likely.

The use of stimulant and nonstimulant medications among individuals with a co-occurring substance use disorder and ADHD has been controversial over the years. The main reason for reluctance to prescribe psychostimulants is their high abuse potential. Another related concern raised by clinicians is that stimulant treatment could worsen the substance use disorder. This has not been shown in clinical trials, and stimulant treatment of ADHD at modest dosages has been shown to reduce substance use as well (87–89). Some of these clinical trials had mixed findings, and their inherent limitations affected the observed outcomes. Such limitations include high treatment discontinuation rate, suboptimal dosing, and low severity of ADHD symptoms at baseline. Chronic substance use dysregulates dopamine neurotransmission, which may require physicians to use doses of methylphenidate and dextroamphetamine that are higher than the standard when treating patients with a substance use disorder and co-occurring ADHD (88, 90, 91).

Although research trials have shown mixed results in the treatment of substance use disorder with co-occurring ADHD, an optimal treatment approach is to consider stimulant medications based on the severity of ADHD symptoms; attend to the risk-benefit analysis; and monitor individuals closely for potential misuse, abuse, and diversion (92–94). Research on methylphenidate (95) and amphetamine formulations (96–99) for the treatment of cocaine dependence and cannabis dependence among ADHD patients has demonstrated that stimulants have a relatively low risk of abuse under monitored conditions. This is especially true for long-acting psychostimulants (89, 92). A study by Cassidy et al. (100) showed that the incidence of diversion and misuse was lower for extended-release amphetamines (0.5%), compared with immediate-release amphetamines (1.1%). The main reasons for the difference are the slow rate of onset and fewer reinforcing effects of long-acting formulations (100).

In some studies, nonstimulant medications, such as atomoxetine, TCAs, bupropion, venlafaxine, monoamine oxidase inhibitors, clonidine, guanfacine, and modafinil, were studied among patients with ADHD and a substance use disorder. Most of these medications were used off label and had limited efficacy in treating ADHD with a co-occurring substance use disorder (101–107).

Although pharmacotherapy remains the main approach to treating ADHD, psychosocial interventions, such as psychoeducation and CBT, can be combined with medications to optimize the long-term management of this disorder (108–110).

The literature about ADHD among patients with a substance use disorder currently shows that treatment has a moderate effect size in reducing ADHD symptoms and substance use. However, long-term treatment should be initiated for high-risk patients, not only to stabilize ADHD symptoms but also to reduce substance use and promote abstinence.

Future Directions

Several pharmacological and nonpharmacological interventions have been designed to treat substance use disorder with co-occurring mental illness. A critical goal is to identify specific therapeutic options that are beneficial for individuals with co-occurring disorders. However, circumstances in both the mental health and the addiction treatment systems make the delivery of optimal health care difficult. A very promising line of research has focused on developing novel treatment approaches for co-occurring disorders.

A double-blind placebo trial by Pettinati et al. (111) that involved patients with depression and co-occurring alcohol use disorders showed that combining sertraline and naltrexone was useful in increasing days abstinent and improving depressive symptoms, compared with treatment with sertraline alone, naltrexone alone, or placebo.

Topiramate, a nonbenzodiazepine anticonvulsant, was studied as a new therapeutic treatment for alcohol use disorder and for other substance use disorders. RCTs (112–114) and a meta-analysis study (115) found topiramate to be associated with a decrease in alcohol dependence, a decline in heavy drinking days, improved quality of life, and reduction in harmful consequences of drinking, compared with placebo. To our knowledge, no study has evaluated topiramate for persons with an alcohol use disorder and a mood disorder. However, limited trials have demonstrated topiramate's efficacy in targeting PTSD symptoms among heavy alcohol users. Alderman et al. (116), in an open-label pilot study involving 29 combat veterans, demonstrated topiramate to be a safe and effective treatment in reducing PTSD symptoms (nightmares and anxiety) and decreasing alcohol consumption. In a prospective randomized study conducted with veterans who had co-occurring alcohol use disorder and PTSD, topiramate showed a reduction in alcohol use, cravings, and PTSD symptoms from baseline to week 12 (117). These two studies showed topiramate to be a promising treatment for PTSD comorbid with alcohol use disorder on the basis of its GABA/glutamate inhibitory action, which is common in both disorders.

Ketamine, a dissociative anesthetic, is a potent *N*-methyl-D-aspartate (NMDA) glutaminergic receptor antagonist that may provide a novel and integrated treatment for substance use disorder with co-occurring mental illness. Meta-analyses have shown ketamine's utility in treating severe depression and suicidal ideation (118–120). This is mainly the result of its effects on glutamate neuromodulation, increased prefrontal synaptic remodeling, and neural plasticity (121–123). This unique effect of ketamine on glutamate regulation has also shown promising results in reduced cravings, decreased self-administration of illicit drugs, and higher rates of abstinence, compared with placebo, for a variety of substance use disorders (124–127). However, the relevance of ketamine in a combined approach for treating comorbid depression and substance use disorder has not been fully explored in clinical trials. Many individuals have co-occurring major depressive disorder and a substance use disorder, and thus ketamine's role as a glutamate modulator and NMDA antagonist in the brain may serve as a therapeutic target for this group.

Noninvasive brain stimulation (NIBS) technologies are becoming increasingly recognized in substance use disorder treatment for their safety, tolerability, and accessibility in modulating neural activity within the brain. Repetitive transcranial magnetic stimulation (rTMS) is an emerging NIBS intervention for treatment of substance use disorders. rTMS applies powerful and focused magnetic field pulses through the skull into the brain, leading to alterations in brain activity (128, 129). Multiple RCTs have shown rTMS to be useful in treating major depressive disorder through enhancement of activity in the dorsolateral prefrontal cortex (DLPFC) of the brain (130–133). Similarly, in treating substance use disorders, rTMS has shown a reduction in craving with a small to medium effect size (134–146). However, its role in treating comorbid major depressive disorder and substance use disorder as a combined approach is limited. In a recent open-label follow-up study, Rapinesi et al. (147) showed that use of high-frequency rTMS applied to bilateral DLPFC through a deep helmet coil yielded a faster response in improving depressive symptoms among patients with co-occurring major depressive disorder and alcohol use disorder, compared with those with major depressive disorder alone. The study also demonstrated reduced alcohol cravings in the group with co-occurring major depressive disorder and alcohol use disorder. However, there were limitations because of the small sample and because sham control groups were not used (147). Because DLPFC is associated with both mood and reward mechanisms (148–151), rTMS focused on DLPFC may be a clinically useful treatment for patients with co-occurring disorders.

Another new treatment approach has focused on studying the usefulness of deep brain stimulation (DBS) in treating psychiatric disorders and substance use disorders. Via surgically implanted microelectrodes, DBS provides continuous stimulation to deeper regions of the brain, compared with rTMS, and is powered by an implantable pulse generator. Originally designed to treat intractable movement disorders, DBS has been successful in treating psychiatric conditions such as treatment-refractory depression and obsessive-compulsive disorder (152–154). Treatment pertaining to DBS in psychiatric illnesses has focused mainly on stimulating the nucleus acumbens and subthalamic nucleus (155). These brain regions are potential targets for the use of DBS in addiction treatment. Studies of DBS for treating substance use disorders is limited to case reports and case series, and thus its efficacy in treating these disorders is unclear. Existing studies suggest that DBS reduces alcohol and drug intake and craving and leads to greater abstinence among alcohol, heroin, and cocaine users (156–161). However, longitudinal studies validating DBS treatment for co-occurring mental and substance use disorders are required, and no RCTs have been published. Moreover, its surgical invasiveness is likely to limit the use of DBS to those with severe psychiatric and substance use disorders.

Taken together, there are numerous promising avenues to pursue. However, clear-cut treatment recommendations using these novel interventions would be premature. Future research is needed to examine the neurobiological mechanisms that may lead to clinical improvement as well as the overall efficacy of these innovative approaches in the various populations with co-occurring disorders.

Conclusions

Mental and substance use disorders co-occur frequently, and the presence of co-occurring disorders may reduce diagnostic certainty. Moreover, individuals with co-occurring disorders require comprehensive treatment approaches. Left untreated, comorbid disorders often lead to worse outcomes than either disorder alone. Research studies and meta-analyses of treatments for co-occurring disorders have reported mixed findings, and current treatment recommendations provide an understanding of how to combine existing therapeutic approaches. Treating co-occurring disorders is feasible and can be effective, but treatment often requires more intensive interventions than with a single disorder. Finally, previous studies may help researchers design future trials to determine the best treatments for co-occurring mental and substance use disorders.

Footnotes

Dr. F. Levin reports serving as a consultant to Major League Baseball. The other authors report no financial relationships with commercial interests.

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