Co-occurring substance use disorder and anxiety-related disorders in adults: Epidemiology, pathogenesis, clinical manifestations, course, assessment, and diagnosis

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INTRODUCTION

Substance use disorder (SUD) commonly co-occurs in anxiety disorders, trauma- and stressor-related disorders, and obsessive compulsive and related disorders [1-5]. The association between these disorders is multifaceted. Anxiety-related disorders may increase the risk for the development of SUDs and may alter the presentation and treatment outcome of SUDs. SUDs may alter the presentation and outcome of treatment for anxiety-related disorders.

The complexity of these comorbidities highlights the importance of a comprehensive understanding of the symptoms of each disorder, proper diagnosis, and use of effective treatments as well as consideration of potentially toxic drug-drug interactions, medication abuse liability, and patient adherence.

This topic reviews the epidemiology, pathogenesis, clinical manifestations, course, and diagnosis of co-occurring SUD and anxiety-related disorders. The treatment of co-occurring SUD and anxiety-related disorders is described separately. Individual anxiety-related disorders and SUDs are described separately.

- (See "Treatment of co-occurring anxiety-related disorders and substance use disorders in adults".)

- (See "Generalized anxiety disorder in adults: Epidemiology, pathogenesis, clinical manifestations, course, assessment, and diagnosis".)
- (See "Social anxiety disorder in adults: Epidemiology, clinical features, assessment, and diagnosis".)
- (See "Panic disorder in adults: Epidemiology, clinical manifestations, and diagnosis".)
- (See "Agoraphobia in adults: Epidemiology, pathogenesis, clinical manifestations, course, and diagnosis".)
- (See "Specific phobia in adults: Epidemiology, clinical manifestations, course, and diagnosis".)
- (See "Posttraumatic stress disorder in adults: Epidemiology, pathophysiology, clinical features, assessment, and diagnosis".)
- (See "Obsessive-compulsive disorder in adults: Epidemiology, clinical features, and diagnosis".)
- (See "Cannabis use and disorder: Epidemiology, pharmacology, comorbidities, and adverse effects".)
- (See "Cocaine use disorder: Epidemiology, clinical features, and diagnosis".)
- (See "Risky drinking and alcohol use disorder: Epidemiology, clinical features, adverse consequences, screening, and assessment".)
- (See "Opioid use disorder: Epidemiology, clinical features, health consequences, screening, and assessment".)
- (See "Benzodiazepine use disorder".)

EPIDEMIOLOGY

Substance use disorders (SUDs) have been found to co-occur at an increased rate in individuals with posttraumatic stress disorder (PTSD), generalized anxiety disorder (GAD), panic disorder, and social anxiety disorder (SAD) compared to rates in the general population. There are mixed findings regarding the co-occurrence of obsessive-compulsive disorder (OCD) and SUDs.

Substance use disorders — The National Epidemiologic Survey on Alcohol and Related Conditions-III assessed 36,309 adults from 2012 to 2013 in the general population using the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Findings show that lifetime and past 12-month prevalence rates for alcohol use disorder, the most common SUD, were 29.1 and 13.9 percent respectively [6]. For drug use disorder, lifetime, and past 12-month prevalence rates were 9.9 and 3.9 percent, respectively [7].

Posttraumatic stress disorder — PTSD, which has an estimated lifetime prevalence of 6.4 to 7.8 percent [8] in United States general population, has been shown to commonly co-occur with

SUDs [9-11]. (See "Posttraumatic stress disorder in adults: Epidemiology, pathophysiology, clinical features, assessment, and diagnosis".)

- The lifetime prevalence of SUDs in persons with non-military PTSD has been reported to range from 21.6 to 43 percent, compared with a range of 8.1 to 24.7 percent in individuals without PTSD [1,9,12,13].

- A study of 2633 individuals in the general United States adult population found that cocaine and opiate users had the highest rates of trauma exposure and PTSD [14]. Similarly, in a 2017 study of 4025 individuals exposed to prescription opioids from the National Epidemiologic Survey on Alcohol and Related Conditions-III, individuals with a baseline PTSD diagnosis were at increased risk of developing an opioid use disorder [15]. Among 170 patients seeking treatment for opioid dependence and chronic pain, 20.6 percent had current PTSD [11].

- In a study of 11,103 adults who endorsed lifetime trauma exposure and alcohol use, bidirectional temporal associations between PTSD and alcohol use disorder were found, indicating that individuals with one of these disorders had increased likelihood of developing the other [16].

Compared with the general population, military personnel are at increased risk of both PTSD and SUDs [17].

- A study of over 88,000 United States veterans returning from the Iraq war found that 16.7 percent had symptoms of PTSD at six months post-deployment [18]. A study of 1822 United States infantry soldiers found that 12 percent screened positive for a diagnosis of PTSD using DSM-5 criteria; in 177 soldiers exposed to combat, 18 percent were positive for PTSD [19].

- In the Millennium Cohort Study, which included over 48,000 military personnel, 53.6 percent reported binge drinking and 15.2 percent reported alcohol related problems [20]. Deployment and exposure to combat were related to increased risk of binge drinking (odds ratio 1.46) and alcohol-related problems (odds ratio 1.63).

- A study of 1120 United States soldiers found that 25 percent screened positive for alcohol misuse three to four months postdeployment [21].

- In a sample of 3157 United States veterans aged 21 and older from the National Health and Resilience Veterans Study, 16.4 percent were positive for probable current PTSD and 14.8 percent were positive for probable current alcohol use disorder. Among those with

probable PTSD, 16.8 percent were also positive for probable alcohol use disorder. Among those with probable alcohol use disorder, 20.3 percent were also positive for probable PTSD [22].

Generalized anxiety disorder — GAD has a lifetime prevalence in the general population of 5.7 percent [23,24]. The likelihood of having GAD has been strongly associated with the presence of alcohol or drug use disorders in data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), which is based on a nationally representative sample in the United States [7,25]. (See "Generalized anxiety disorder in adults: Epidemiology, pathogenesis, clinical manifestations, course, assessment, and diagnosis".)

Across several studies, the prevalence of GAD among patients with a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) alcohol use disorder ranged from 8.3 to 52.6 percent [26]. Data from the National Comorbidity Study (NCS), a nationally representative sample of United States adults, found an association between lifetime GAD and lifetime use of stimulants (odds ratio 2.07), cocaine (odds ratio 2.39), hallucinogens (odds ratio 5.09), and heroin (odds ratio 4.27) [27]. Data from one study of treatment-seeking individuals with DSM-IV opioid dependence found that 15.9 percent had current GAD [11].

Panic disorder — Data from the Epidemiological Catchment Area study in five United States cities found a lifetime prevalence of panic disorder among adults of 1.5 percent [28]. Thirty-six percent of patients with panic disorder were additionally diagnosed with an SUD. In a cross-national epidemiologic study of DSM-5 panic disorder and panic attacks in 25 different countries, lifetime prevalence of panic disorder was 1.7 percent, and lifetime prevalence of panic attacks was 13.2 percent. The majority (80.4 percent) of those with lifetime panic disorder had at least one comorbid mental health disorder. Among those with panic disorder, 26.2 percent had a comorbid SUD [29]. (See "Panic disorder in adults: Epidemiology, clinical manifestations, and diagnosis".)

Data from four large epidemiological surveys found that the estimated lifetime risk of panic disorder in individuals with DSM-IV diagnoses of alcohol abuse or dependence ranged from 0.97 to 3.82 percent, compared to individuals without an SUD [28,30-33]. A study of 1071 subjects participating in the National Household Survey on Drug Abuse in the United States estimated that cocaine use was associated with a 3.3-fold excess occurrence of panic attacks [34]. The lifetime prevalence of panic disorder with and without agoraphobia among patients with an opiate use disorder was 5 percent and 14 percent, respectively [35]. A prospective study of 2548 young adults found that panic disorder was a significant predictor of hazardous alcohol use and the persistence of alcohol use disorder [36]. The presence of a lifetime diagnosis of drug use disorder was associated with panic disorder [7].

Social anxiety disorder — Two studies of nationally representative samples in the United States estimated the lifetime prevalence of SAD to range from 5.0 to 13.3 percent and the 12-month prevalence to range from 2.8 to 7.9 percent [1,37]. Alcohol use disorders in individuals with SAD were common, for example, the NESARC found a 48 percent lifetime prevalence [37]. A study demonstrated modestly increased associations between lifetime SAD and lifetime stimulant, cocaine, hallucinogen, and heroin use (odds ratios 1.86, 1.45, 2.3, and 1.6 respectively) [27]. A strong association has been observed between SAD and marijuana use. The NCS found that individuals with SAD are seven times more likely to have a DSM-IV diagnosis of marijuana dependence than individuals without SAD [38]. (See "Social anxiety disorder in adults: Epidemiology, clinical features, assessment, and diagnosis".)

Individuals with SAD are highly vulnerable to SUDs [27]. Data on 8841 patients with SAD from the Australian National Survey of Mental Health and Wellbeing found that SAD is the most common anxiety disorder among individuals with SUDs (33.3 to 36.0 percent) [10]. Research shows that socially phobic individuals are two to three times more likely than individuals without SAD to develop an alcohol use disorder [26]. The onset of SAD typically precedes the development of the SUD [39], and up to 16.4 percent of socially phobic individuals endorse self-medicating anxiety symptoms with alcohol and drugs [40]. A prospective study of 627 individuals found that SAD was associated with the subsequent onset of alcohol use disorder; PTSD was associated with a subsequent onset of an SUD [41].

Obsessive-compulsive disorder — There is mixed evidence for whether individuals with OCD have a higher rate of co-occurring SUDs than the general population:

- A large epidemiological study of six geographic areas in the United States found no difference between rates of OCD among individuals with a DSM-IV diagnosis of alcohol dependence compared with a control group without alcohol dependence [42].
- Two studies of patients receiving psychiatric treatment in the United States found that 1.3 to 4.0 percent of patients with OCD met criteria for a lifetime SUD [43,44].
- In contrast, a survey of 25,097 adults from the Canadian Community Health Survey found that individuals with OCD were significantly more likely to have current (past 12 months) and lifetime alcohol and drug use disorders compared with individuals without OCD [45].
- A smaller survey study of 430 undergraduate students in the United States found that increased OCD symptom severity was associated with increased cannabis misuse [46].

PATHOGENESIS

Emergent data suggest that substance use disorders (SUDs) and anxiety disorders share common neurobiological substrates that include the hypothalamic pituitary adrenal (HPA) axis and noradrenergic system.

Hypothalamic pituitary adrenal (HPA) axis — While the findings on HPA axis reactivity are mixed, a preponderance of evidence suggests that a disruption in normal HPA hormonal feedback is a common physical feature of both substance use and anxiety disorders. More specifically, these studies suggest that a hyperactive HPA axis occurs as a function of long-term drug use and/or prolonged stress exposure.

The HPA axis has been implicated in behaviors associated with an SUD. As an example, stress is a powerful predictor of relapse, and perturbations within the HPA axis as a result of long-term drug exposure are hypothesized to culminate in an addictive phenotype [47,48]. Even acute drug exposure in drug-naïve humans and rodents increases circulating HPA hormone levels [49]. Clinical studies of men and women with a diagnosis of cocaine dependence demonstrate that corticotropin releasing hormone (CRH) promotes drug craving and subjective stress [50].

Studies of posttraumatic stress disorder (PTSD) and HPA axis reactivity are complex and have yielded equivocal findings [51]. Findings from studies of patients with PTSD have been mixed. For example, compared with healthy controls, patients with PTSD have higher, lower and normal 24-hour urinary cortisol levels [52-54]. However, the majority of studies support enhanced glucocorticoid negative feedback in patients with PTSD, suggesting a hyperactive physiological stress system. As an example, clinical studies have shown elevated lymphocyte glucocorticoid receptor levels in patients with PTSD and enhanced suppression of cortisol following a dexamethasone challenge, as well as elevated ACTH levels following a metyrapone challenge [55-57]. Patients with PTSD exhibit higher levels of cerebral spinal fluid CRH than healthy controls. The hyperactive HPA hormonal response is thought to be involved in hyperarousal that is commonly observed in PTSD patients [58].

Studies of the HPA axis in individuals with panic disorder, generalized anxiety disorder (GAD), and social anxiety disorder (SAD) have been inconclusive. As an example, one study found that individuals with panic disorder exhibited a similar HPA hormone response to metyrapone and metyrapone plus dexamethasone as controls [59]. Another study found higher diurnal cortisol levels in individuals with panic disorder than controls [60]. Elevated [61] and normal [62] basal cortisol levels have been reported among individuals with GAD. Dexamethasone challenge results in patients with GAD are difficult to interpret, as greater non-suppression [63] and normal suppression [64] have been reported. Similar salivary cortisol levels were found between patients with SAD and healthy controls following electrical stimulation [65].

Findings regarding HPA axis functioning in patients with obsessive-compulsive disorder (OCD) are mixed. As an example, both cortisol suppression and nonsuppression have been found in OCD patients in response to a dexamethasone challenge [66,67]. Both higher [68] and normal CRH [69] levels have been reported in the cerebral spinal fluid of OCD patients [68,69]. However, other studies have been more conclusive demonstrating elevated cortisol, dehydroepiandrosterone, and ACTH concentrations and higher 24-hour urinary cortisol levels in OCD patients [70-72].

Noradrenaline systems — Animal models of addiction have demonstrated that norepinephrine plays a critical role in the transition from recreational drug use to an SUD [73]. Dopamine beta-hydroxylase inhibitors attenuate alcohol intake in rodents [74]. Alpha1-noradrenergic receptor antagonists prevent escalation of drug seeking behavior [75,76]. Noradrenergic activity has been linked to anxiety and negative affect during opiate withdrawal [77]. Noradrenergic activity has been associated with drug craving and relapse in cocaine-dependent individuals [78,79].

Compared with healthy controls, PTSD patients have a lower number of platelet positive alpha2-adrenergic receptors, and higher 24-hour urinary norepinephrine levels. Compared with controls, PTSD patients showed increases in salivary alpha amylase upon awakening. Patterns of salivary alpha amylase secretion were positively associated with symptoms of PTSD [80]. PTSD patients exhibit a sensitized cardiovascular response to the alpha2-receptor antagonist yohimbine [81]. Medications that attenuate noradrenergic activity have been the used to treat symptoms of PTSD [82,83].

The strongest evidence for a role of noradrenergic systems in mediating symptoms of GAD may be from pharmacotherapy trials, which have found serotonin- norepinephrine reuptake inhibitors (SNRIs) to be effective in the treatment of GAD [84]. (See "Generalized anxiety disorder in adults: Management", section on 'Initial Pharmacotherapy'.)

Yohimbine produces panic-like symptoms in healthy controls [85]. Administration of yohimbine to individuals with panic disorder caused greater increases in norepinephrine turnover than in healthy controls [86]. SNRIs are clinically effective at attenuating symptoms of panic disorder [87]. Patients with SAD exhibit greater salivary alpha amylase in response to electrical stimulation compared with healthy controls [65]. (See "Management of panic disorder with or without agoraphobia in adults".)

Few, limited studies have examined noradrenergic dysregulation in patients with OCD, with inconclusive results. Data from the existing studies are inconclusive. A study found no difference in behavioral or noradrenergic responses to yohimbine between OCD patients and

healthy controls [88]. Another study has shown elevated plasma norepinephrine levels in OCD patients [89].

CLINICAL MANIFESTATIONS

Individuals with a co-occurring substance use disorder and an anxiety-related disorder on average present with a more severe clinical profile as compared to individuals with either disorder alone [90,91]. As an example, research involving individuals seeking treatment has demonstrated that individuals with DSM-IV cocaine dependence and posttraumatic stress disorder (PTSD), as compared to individuals without PTSD, present with more severe depression, vocational impairment, interpersonal dysfunction, medical problems, and other Axis I and II disorders.

Substance use, physiologic dependence, and withdrawal can mimic or exacerbate symptoms of anxiety.

- Stimulants, in particular, can cause heart palpitations, trembling or shaking, sweating, dizziness or feeling faint, depersonalization, paresthesias, nausea, and hot flushes.
- Withdrawal from substances such as opioids, alcohol, and benzodiazepines, can generate anxiety symptoms.
    - Opiate withdrawal is characterized by insomnia, nausea, and diarrhea, but may be distinguished from independent anxiety by the often severe muscle aches, vomiting and fever. (See "Opioid withdrawal in the emergency setting".)
    - Alcohol and benzodiazepine withdrawal may also generate anxiety symptoms, such as insomnia, psychomotor agitation, tachycardia, perspiration, nausea, and tremor. (See "Management of moderate and severe alcohol withdrawal syndromes".)

COURSE

The median age of onset for DSM-IV diagnoses of alcohol and other drug dependence has been estimated at 23 and 21 years of age, respectively [24]. The median age of onset for anxiety-related disorders ranges from 7 years old for specific phobia to 31 years old for generalized anxiety disorder. However, a 2018 study of 13,984 college students from eight countries found a median age of onset of 15.6 years for alcohol use disorders and 16.2 years for SUD. Average age of onset for both GAD and panic disorder was 14.9 years old. The authors suggest that the

discrepancy in age of onset in these results compared with the National Comorbidity Survey Replication [24] results may be related to several factors including the range of age of the sample for each study (college students versus 18 to 65 years old) [92].

In the majority of cases, the anxiety-related disorder is temporally primary, meaning that the onset of the anxiety-related disorder precedes the onset of the substance use disorder (SUD) [2,16,26,93]. An analysis of data from several epidemiologic studies found that among individuals with DSM-IV diagnoses of both alcohol dependence and an anxiety disorder, the anxiety disorder preceded alcohol dependence in 56.7 to 79.4 percent of cases [94]. Among individuals with DSM-IV diagnoses of both drug dependence and an anxiety disorder, the anxiety disorder preceded drug dependence in 67.6 percent to 100 percent of cases [94].

This temporal ordering of onset suggests that anxiety-related disorders predispose individuals to developing SUDs later in life; however, available evidence does not allow for definitive conclusions on causality [26,93]. This link between anxiety-related disorders and SUDs may be related to self-medication of anxiety symptoms, shared neurobiological connections, or genetic predispositions.

Both SUDs and anxiety-related disorders are chronic, relapsing conditions. Comorbid SUDs and anxiety-related disorders are more chronic than non-comorbid substance use or anxiety-related disorders, and are associated with increased likelihood of poverty, homelessness, being the victim or perpetrator of abuse, and risk of death by homicide, suicide or accidental means [2,22].

ASSESSMENT AND DIAGNOSIS

Differentiating diagnostically between a substance-induced state and a true anxiety-related disorder needs to be addressed in the psychiatric examination. Most of the time, however, the co-occurring anxiety disorder will be independent and will not be a substance-induced anxiety disorder. In patients with a co-occurring substance use disorder (SUD) and independent anxiety-related disorder from a nationally representative sample of the United States population, only a few individuals experienced current anxiety disorders that were only substance induced. These findings strongly suggest that co-occurring anxiety-related disorders among patients with a SUD be targeted in treatment. Otherwise, the anxiety symptoms will continue to serve as a trigger for relapse [4].

Presentations can be challenging to diagnose due to several areas of overlapping manifestations:

- The active use of some substances, such as stimulants, may produce anxiety states that mimic true anxiety disorders.
- Withdrawal from some substances, such as opiates and benzodiazepines, lead to anxiety states.
- The chronic use of drugs and alcohol exerts a powerful influence on neurotransmitter systems related to the development of anxiety-related disorders, and may unmask a biological susceptibility or lead to neurobiologic changes over time that manifest as anxiety disorders.

Clinical assessment needs to consider illicit drugs, caffeine, nicotine, and over-the-counter medications such as pseudoephedrine and diet pills, all of which may produce substantial anxiety, irritability and panic attacks [95], and mimic the symptoms of panic disorder and drug withdrawal [96,97]. Decreasing consumption of these substances may help to significantly decrease anxiety. As an example, patients with panic disorder may find that reducing their consumption of caffeinated sodas, coffees and teas leads to a decrease in the frequency and severity of their panic attacks.

Clinical observation during a period of abstinence from substances can distinguish a substance-induced, transient state from a true anxiety disorder. The duration of abstinence necessary for accurate diagnosis varies depending on the substance.

- For substances with a long half-life (eg, benzodiazepines such as clonazepam, methadone), withdrawal symptoms may be protracted. Several weeks of abstinence may be needed to distinguish anxiety stemming from withdrawal from an independent anxiety disorder [98].
- For substances with a shorter half-life (eg, alcohol and cocaine), accurate diagnosis may be possible after a shorter period of abstinence (eg, 30 days) [99].

Several questions may help differentiate between a substance-induced state and a true anxiety disorder. Endorsement of the following questions supports a primary anxiety diagnosis:

- Were the anxiety symptoms present before substance use commenced?
- Were anxiety symptoms present during periods of sobriety greater than one to three months?
- Is there a positive family history of anxiety disorders?

Generalized anxiety disorder — Generalized anxiety disorder (GAD) in particular can be difficult to diagnose in the presence of active substance use. Symptoms of GAD, which include anxiety, worry, restlessness, fatigue, irritability, poor concentration, muscle tension, and sleep impairment, can be mimicked by substance use. To accurately diagnose GAD, the assessment should be delayed until intoxication or withdrawal has terminated. Reassessment of the patient after a period of prolonged abstinence can confirm the diagnosis. (See "Generalized anxiety disorder in adults: Epidemiology, pathogenesis, clinical manifestations, course, assessment, and diagnosis".)

Early identification of drug or alcohol use among patients with GAD is critical, because GAD is associated with significantly faster progression from initial substance use to the development of an SUD. In a study of 1,269 adolescents and young adults, GAD was associated with a 3.5-fold increase in rate of progression from first drink to the onset of alcohol dependence [100].

Obsessive-compulsive disorder — Obsessive-compulsive disorder (OCD) has symptoms that overlap with SUDs. However, while SUDs are characterized by elements of obsessive thinking and compulsive behaviors [101], a diagnosis of OCD is differentiated by the focus of the obsessions and compulsions. Patients with OCD endorse thoughts centered on contamination or doubt. Patients with SUDs endorse intrusive thoughts centered on alcohol or drugs, feel compelled to use alcohol or drugs, and may feel that if they use substances, the distressing thoughts or compulsions to use will be quelled. The use of substances is connected in a realistic way with the cravings that patients with SUDs experience. (See "Obsessive-compulsive disorder in adults: Epidemiology, clinical features, and diagnosis".)

Panic disorder — Differential diagnosis of panic disorder and SUDs can be complicated by the fact that acute intoxication or withdrawal from alcohol, stimulants, and opioids can precipitate panic-like symptoms [102]. (See "Panic disorder in adults: Epidemiology, clinical manifestations, and diagnosis", section on 'Assessment'.)

As examples:

- Heavy alcohol use increases sensitivity to carbon dioxide, thereby increasing the possibility of a panic attack [103].
- Because of noradrenergic stimulation, the use of stimulants may induce panic attacks [104].
- Anxiety is observed during withdrawal from sedatives.

Other anxiety disorders — Substance-induced anxiety can be distinguished from social anxiety disorder (SAD) by the latter's requirement for the presence of a fear of public scrutiny, which is not mimicked by substance use, intoxication, or withdrawal. In addition, symptoms of SAD usually present early in life, before the onset of substance use. (See "Social anxiety disorder in adults: Epidemiology, clinical features, assessment, and diagnosis", section on 'Diagnosis'.)

Posttraumatic stress disorder — Symptoms of posttraumatic stress disorder (PTSD) result from exposure to a traumatic life event (eg, physical or sexual assault, natural disaster, serious accident, combat experiences). Intrusive thoughts or images related to the trauma are unlikely to be mimicked by substance use, intoxication or withdrawal. Hyperarousal symptoms of PTSD (eg, irritability, sleep impairment, difficulty concentrating, exaggerated startle response) as well as negative alterations in mood and cognition can be mimicked or exacerbated by the use of or withdrawal from alcohol and drugs. (See "Posttraumatic stress disorder in adults: Epidemiology, pathophysiology, clinical features, assessment, and diagnosis", section on 'Diagnosis'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Opioid use disorder and withdrawal" and "Society guideline links: Benzodiazepine use disorder and withdrawal" and "Society guideline links: Alcohol use disorders and withdrawal" and "Society guideline links: Stimulant use disorder and withdrawal" and "Society guideline links: Cannabis use disorder and withdrawal" and "Society guideline links: Anxiety and anxiety disorders in adults".)

SUMMARY AND RECOMMENDATIONS

- Substance use disorders (SUDs) have been found to co-occur at an increased rate in posttraumatic stress disorder (PTSD), generalized anxiety disorder (GAD), panic disorder, and social anxiety disorder (SAD). In most instances, the anxiety disorder onset precedes that of the SUD(s). Results regarding obsessive-compulsive disorder (OCD) and SUDs are mixed. (See 'Epidemiology' above.)

- Preclinical studies demonstrate that SUDs and anxiety-related disorders share common neurobiological substrates that include disruptions within the hypothalamic-pituitary-adrenal (HPA) axis and noradrenergic systems. (See 'Pathogenesis' above.)

- Individuals with co-occurring SUDs and anxiety-related disorders present with a more severe clinical profile and greater chronicity as compared to individuals with either

disorder alone. (See 'Clinical manifestations' above and 'Course' above.)

- Clinical observation during a period of prolonged abstinence from substances can distinguish a transient, substance-induced state from a true anxiety disorder. The duration of abstinence necessary for accurate diagnosis varies depending on the substance. (See 'Assessment and diagnosis' above.)
  - Substances with a long half-life (eg, clonazepam, methadone) may require several weeks of abstinence to make an accurate diagnosis.
  - Substances with a shorter half-life (eg, alcohol and cocaine), can generally be accurately diagnosed after approximately 30 days of abstinence.
- Tips for distinguishing anxiety-related disorders from the effects of substance intoxication or withdrawal differ by disorder:
  - Most of the symptoms of generalized anxiety disorder can be mimicked by substance use. Assessment should be delayed until symptoms of intoxication or withdrawal have resolved. (See 'Generalized anxiety disorder' above.)
  - In contrast with OCD, obsessive thinking and compulsive behaviors that occur secondary to a SUD center on the substances used. (See 'Obsessive-compulsive disorder' above.)
  - Substances, stimulants in particular, can induce panic attacks. In contrast to panic experienced in the context of SUDs, attacks characteristic of panic disorder occur unexpectedly, and patients experience persistent worry about having another attack. (See 'Panic disorder' above.)
  - Hyperarousal symptoms of PTSD (eg, irritability, sleep impairment, difficulty concentrating, exaggerated startle response) can be exacerbated by the use of, or withdrawal from, alcohol and drugs. (See 'Other anxiety disorders' above.)
  - The primary feature of SAD, fear of public scrutiny, is not typically mimicked by substance use, intoxication, or withdrawal. Symptoms of SAD that present only in the context of intoxication or withdrawal are not sufficient to meet criteria for a diagnosis of SAD. (See 'Other anxiety disorders' above.)

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