Treatment of co-occurring anxiety-related disorders and substance use disorders in adults

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INTRODUCTION

Substance use disorders (SUDs) are common in patients with concurrent anxiety-related disorders (ie, anxiety disorders, posttraumatic stress disorder and obsessive-compulsive disorder) [1-4]. The association between SUDs and anxiety-related disorders is multifaceted. Some anxiety-related disorders are associated with increased risk for the development of SUD and may alter the presentation and treatment outcomes of SUD [5]. SUD may alter the presentation and outcome of treatment for anxiety-related disorders.

The complexity of these comorbidities highlights the importance of recognizing the symptoms of each disorder and diagnosing them accurately. Effective treatment requires consideration of potentially toxic drug-drug interactions, medication misuse liability, and patient adherence. Evidence from clinical trials of treatments for the disorders when presenting individually is generally inadequate to determine treatment effectiveness for anxiety disorders and SUD when presenting concurrently.

In the revision of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), diagnoses of substance abuse and substance dependence in DSM-IV were replaced by the single diagnosis of substance use disorder in DSM-5 [6].

This topic reviews treatment of co-occurring anxiety-related disorders and substance use disorders. The epidemiology, pathogenesis, clinical manifestations, course, and diagnosis of anxiety-related disorders co-occurring with SUD and noncomorbid anxiety-related disorders are reviewed separately. (See "Co-occurring substance use disorder and anxiety-related disorders in adults: Epidemiology, pathogenesis, clinical manifestations, course, assessment, and diagnosis" and "Generalized anxiety disorder in adults: Epidemiology, pathogenesis, clinical manifestations, course, assessment, and diagnosis" and "Social anxiety disorder in adults: Epidemiology, clinical features, assessment, and diagnosis" and "Panic disorder in adults: Epidemiology, clinical manifestations, and diagnosis" and "Obsessive-compulsive disorder in adults: Epidemiology, clinical features, and diagnosis" and "Posttraumatic stress disorder in adults: Epidemiology, pathophysiology, clinical features, assessment, and diagnosis".)

Treatment of individual, noncomorbid anxiety-related disorders are also reviewed separately. (See "Management of panic disorder with or without agoraphobia in adults" and "Obsessive-compulsive disorder in adults: Psychotherapy" and "Management of obsessive-compulsive disorder in adults" and "Psychotherapy for panic disorder with or without agoraphobia in adults" and "Posttraumatic stress disorder in adults: Psychotherapy and psychosocial interventions" and "Approach to treating social anxiety disorder in adults" and "Generalized anxiety disorder in adults: Management" and "Posttraumatic stress disorder in adults: Treatment overview".)

Treatment of individual, noncomorbid substance use disorders are also reviewed separately. (See "Cannabis use disorder: Clinical features, screening, diagnosis, and treatment" and "Alcohol use disorder: Pharmacologic management" and "Alcohol use disorder: Psychosocial management" and "Brief intervention for unhealthy alcohol and other drug use: Efficacy, adverse effects, and administration" and "Benzodiazepine use disorder" and "Opioid use disorder: Treatment overview" and "Stimulant use disorder: Treatment overview".)

APPROACH TO TREATMENT

In patients with co-occurring anxiety-related disorders, it is necessary to treat both disorders. Treating the substance use disorder (SUD) without addressing the anxiety-related disorders may render the patient vulnerable to relapse in the face of anxiety symptoms. Treating the anxiety-related disorders without addressing and monitoring the SUD will likely result in ineffective, or even harmful, treatment.

Anxiety symptoms may undermine treatment outcome by serving as a trigger for relapse. SUD patients need to learn skills for managing and/or accepting anxiety or trauma-related

symptoms without using substances. As an example, patients with panic disorder who complete exposure or other anxiety-provoking homework assignments while under the influence of alcohol or drugs will not experience the natural rise and fall of anxiety during those assignments, nor will they learn corrective information that the anxiety does not last forever and they are able to withstand anxiety symptoms without using alcohol or drugs.

Based on limited data from clinical trials and our clinical experience, we suggest first-line treatment of most adults with an anxiety disorder and a co-occurring SUD with integrated cognitive-behavioral therapy (CBT) that addresses both disorders rather than other treatments. The evidence in support of this combined intervention is limited and has yielded mixed results. (See 'Integrated CBT' below.)

For patients with co-occurring posttraumatic stress disorder and SUD, we suggest first-line treatment with a trauma-focused integrated CBT that includes exposure rather than other psychotherapy. (See 'Posttraumatic stress disorder' below.)

For patients who prefer medication rather than CBT, or if CBT is unavailable, treatment of the anxiety-related disorder with a selective serotonin reuptake inhibitor (SSRI) or a serotonin-norepinephrine reuptake inhibitor (SNRI) are reasonable alternatives. In such cases, the SUD should be treated as well.

We suggest combined treatment with integrated CBT and an SSRI rather than either intervention as monotherapy in patients with a co-occurring anxiety-related disorder and an SUD if the (see 'Integrated CBT' below):

- Anxiety-related disorder has previously responded to an SSRI
- Anxiety-related disorder is severe and disabling
- Disorders are accompanied by other comorbidities (eg, depression)
- Disorders fail to respond adequately to either modality as monotherapy

Other medications are used to treat anxiety-related disorders that do not adequately respond to SSRIs/SNRIs and to treat SUDs. Selection of medications for treatment of co-occurring anxiety-related disorders and SUDs needs to take into account the abuse potential of medications prescribed, as well as the potential for toxic interactions between the medications and alcohol/drugs, and between the medications and medical conditions caused by alcohol/drugs. In addition, clinicians should proactively address the increased risk of nonadherence to prescribed medications often seen in this patient population. (See 'Pharmacotherapy' below.)

Medication may be needed early on, particularly to help reduce anxiety or trauma-related symptoms while the patient is mastering behavioral ways of coping with the symptoms, if there are withdrawal symptoms that will lead to relapse, and to help increase retention. Pharmacotherapies that address substance use withdrawal and craving may be useful in addition to integrated CBT.

Accumulating research evidence has challenged past beliefs that patients with a co-occurring anxiety-related disorder and SUD had to be abstinent from alcohol/drugs for an extended period (eg, three to six months) before treating the anxiety-related disorder. As an example, trials of treatment for patients with posttraumatic stress disorder and SUD found that addressing the trauma early in treatment results in significant improvements in posttraumatic stress disorder symptoms as well as alcohol and drug use [7-14]. In our clinical work with outpatients with an anxiety-related disorder and an SUD, we have increasingly shifted to initiating treatment upon their presentation to our clinic, unless hospitalization is first needed for a medically supervised withdrawal.

INTEGRATED CBT

Integrated cognitive-behavioral therapy (CBT) combines cognitive and behavioral interventions for both anxiety-related disorders and co-occurring substance use disorders (SUDs) [15]. The components of integrated CBT in these disorders have varied in published trials, but typically include:

- Education and coping skills training for both disorders
- Exposure or other behavioral interventions for the anxiety disorder
- Relapse prevention for SUDs in patients who have achieved abstinence

Clinical trials of integrated CBT for co-occurring anxiety-related disorders and SUDs have found positive results for obsessive-compulsive disorder (OCD), mixed results in panic disorder, and negative results for social anxiety disorder (SAD). Many more trials have been conducted in patients with posttraumatic stress disorder (PTSD). Interventions including exposure resulted in reductions in PTSD symptoms without worsening of substance use, but SUD outcomes were mixed.

Generalized anxiety disorder — There are no clinical trials of integrated interventions targeting both generalized anxiety disorder and SUDs.

Social anxiety disorder — A clinical trial did not find an integrated CBT intervention to be effective in patients with co-occurring social SAD and SUD. The trial randomly assigned 93

patients with SAD and the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) alcohol dependence to receive individual CBT for alcohol dependence only, or an individual, integrated CBT addressing both disorders [16]. The group receiving integrated psychotherapy for both alcohol and social anxiety disorders had worse outcomes on three of the four alcohol use indices, and no differences were seen between groups on measures of social anxiety.

Panic disorder — A clinical trial with 231 patients with co-occurring panic disorder and DSM-IV alcohol dependence receiving inpatient treatment for the SUD did not find the addition of group CBT for panic disorder to improve outcomes for either condition [17]. While both groups experienced improvement, no differences were seen between the CBT and non-CBT groups on most measures of panic disorder symptoms and alcohol use at 3, 6, and 12 months post-treatment.

Obsessive-compulsive disorder — In a randomized clinical trial of patients with co-occurring OCD and SUD, a combined cognitive and behavioral intervention led to improvement in both disorders [18]. The trial randomly assigned 60 patients with co-occurring OCD and an SUD to either exposure and response prevention therapy (a type of CBT used for OCD) in conjunction with behavioral therapy for the SUD, behavioral therapy for the SUD only, or behavioral therapy for the SUD combined with progressive muscle relaxation (as a control intervention). The group receiving CBT for OCD and behavioral therapy for the SUD experienced a greater reduction in OCD symptoms, a higher abstinence rate, and greater treatment retention compared with the other two groups.

Posttraumatic stress disorder — Multiple meta-analyses have found integrated, trauma-focused CBT to be efficacious for patients with both PTSD and SUDs [12,13]. Exposure-based therapies led to larger reductions in PTSD symptoms compared with nonexposure therapies. Exposure did not appear to increase substance use or relapse. In general, improvement in PTSD symptoms was seen more consistently compared with improvement in SUD outcomes.

A 2015 meta-analysis in 14 trials with 1506 participants found that individual (not group) trauma-focused CBT interventions, typically including exposure and delivered alongside an SUD intervention, were more effective for comorbid PTSD and SUD compared with treatment as usual or other comparison conditions [12]. Little evidence for non-trauma-focused interventions in individual or group formats was observed. Integrated treatments for PTSD and SUDs were associated with a decrease in substance use.

A 2017 review examined 24 randomized clinical trials with 2294 participants of behavioral interventions for comorbid PTSD and SUD [13]. The interventions were categorized as:

- Exposure-based interventions
- Coping-based interventions
- Addiction-focused interventions

For reducing PTSD symptoms, exposure-based treatments were the most effective type of intervention. For reducing SUD severity, most of the trials did not show a difference in outcomes between exposure-based treatment and the control condition. Approximately 50 percent of participants with PTSD and SUD completed treatment, without differences in rates across the three treatment modalities.

Several integrated CBT programs have been tested, including trauma-focused PTSD interventions and non-trauma-focused, both with and without exposure:

- **Concurrent treatment of PTSD and SUD using prolonged exposure (COPE)** – COPE is a manualized, 12-session, individual treatment that integrates prolonged exposure therapy (imaginal and in vivo exposure) for PTSD and CBT for SUD:

  - Sessions 1 to 2 focus on psychoeducation regarding the interrelationship between PTSD and SUD, coping with cravings and triggers for use (both substance and trauma-related triggers), and the rationale for prolonged exposure.

  - Sections 3 to 12 include in vivo exposures.

  - Sessions 4 to 11 include imaginal exposures.

  - SUD topics are weaved throughout the treatment; for example, managing thoughts about using, high-risk situations, and drink/drug refusal skills.

  Multiple randomized trials demonstrate the efficacy of COPE in reducing PTSD in patients with co-occurring PTSD and SUD compared with other active treatments or control conditions [8,10,14,19-22]. Overall, patients who were randomized to COPE experienced lower PTSD symptoms at post-treatment and higher rates of PTSD diagnostic remission, compared with control conditions. SUD severity tended to decrease comparably between patients who received COPE versus an SUD-only intervention.

  As examples:

  - A 2019 randomized trial compared COPE versus Seeking Safety among 119 military veterans with PTSD and alcohol use disorder. COPE resulted in greater reduction in PTSD symptom severity and higher rates of PTSD diagnostic remission, and evidenced comparable reduction in substance use [21]. The number of days abstinent roughly

doubled from baseline to end of treatment in both groups. Average number of sessions completed was lower in COPE compared with Seeking Safety (8 versus 11). Even with fewer sessions, COPE, an exposure-based therapy, was more efficacious than Seeking Safety, which does not include exposure.

- A 2019 trial compared COPE and relapse prevention therapy in 81 military veterans with PTSD and SUDs [20]. COPE led to greater reductions in PTSD severity and higher rates of PTSD diagnostic remission compared with relapse prevention therapy. SUD severity comparably decreased in both groups during treatment. At six months follow-up, the COPE group evidenced fewer drinks per drinking day (approximately four fewer drinks per day) compared with the relapse prevention group.

- **Prolonged exposure therapy –** Prolonged exposure therapy reduced PTSD symptoms in a clinical trial of patients with opioid use disorder and PTSD [23]. The trial randomly assigned 52 individuals with PTSD and opioid use disorder to receive a modified version of prolonged exposure (ie, sessions were 60 minutes, breathing relaxation was conducted at the end of each imaginal exposure) or a nontrauma-focused comparison intervention. At the end of the trial, the group assigned to modified prolonged exposure experienced greater reductions in PTSD symptoms, sleep disturbances, and symptoms of anxiety and depression.

- **Substance Dependence PTSD Therapy (SDPT)** – SDPT is a five-month, twice-weekly, manualized individual CBT utilizing relapse prevention and coping skills training for SUD, and psychoeducation, stress inoculation training, and in vivo exposure for PTSD [24]. A small randomized trial compared SDPT with 12-step facilitation therapy in the treatment of 19 patients with IV cocaine use disorder and PTSD [25]. No difference was seen between treatment groups on outcomes of substance misuse or PTSD symptoms. Retention in treatment was better in the SDPT group compared with the 12-step facilitation group (median of 26 versus 16 sessions).

- **Seeking safety** – Seeking safety, a manualized, non-trauma-focused integrated CBT provides psychoeducation and coping skills. The intervention includes 24-session topics and was initially designed for group therapy but has also been tested in an individual format. Randomized trials in women with PTSD and SUDs have shown mixed evidence of efficacy for Seeking Safety [19,26-29]. As examples:

  - A 2019 multisite clinical trial randomly assigned 343 women with PTSD and SUD to either Seeking Safety plus treatment as usual, relapse prevention therapy plus

treatment as usual, or treatment as usual [19]. No differences in PTSD or SUD outcomes were observed among groups.

- A 2018 clinical trial with 52 veterans with PTSD and SUD compared Seeking Safety with an alternative CBT intervention, Creating Change, which includes exploration of past trauma memories [29]. Results showed both conditions resulted in comparable improvement in PTSD, substance use, and quality of life with no between-group differences.

Other integrated CBT models have been tested in patients with PTSD and SUD [30]. A review article of clinical trials of cognitive processing therapy found the integrated treatment to be safe and well tolerated by patients.

PHARMACOTHERAPY

With the exception of comorbid posttraumatic stress disorder (PTSD) and substance use disorders (SUDs), there are very few prospective studies of combined treatment of an SUD with a comorbid anxiety disorder.

SSRIs and SNRIs — Many of selective serotonin and norepinephrine reuptake inhibitors (SSRIs and SNRIs) are US Food and Drug Administration (FDA)-approved treatments for several anxiety disorders including generalized anxiety disorder and social anxiety disorder, as well as related disorders such as PTSD and obsessive-compulsive disorder; however, there are several potential drug interactions with alcohol or drugs.

- Use of SSRIs and SNRIs in conjunction with 3-4 methylenedioxymethamphetamine (MDMA), opioids, cocaine, and amphetamines increases the risk of serotonin syndrome, a potentially lethal adverse event characterized by hyperthermia, diaphoresis, agitation, diarrhea, tremor, hyperreflexia, dilated pupils, and seizures [31].

- These findings suggest that SSRIs and SNRIs may be safer in abstinent individuals compared with individuals with ongoing substance use.

A 2015 Cochrane systematic review and meta-analysis of pharmacotherapy for co-occurring anxiety and alcohol use disorders found no evidence that alcohol use was responsive to medication [32].

- Paroxetine has been shown in several studies to reduce social anxiety but not alcohol consumption in individuals with co-occurring alcohol use disorder [33-35]. As an example, a clinical trial randomly assigned 15 individuals meeting the American Psychiatric

Association's Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for both social anxiety disorder and alcohol use disorder to receive paroxetine or placebo for eight weeks [33]. Patients treated with paroxetine improved more than those treated with placebo on both the Clinical Global Index and the Liebowitz Social Anxiety Scale. No change was seen in the quantity or frequency of drinking.

- Some clinical trials have found SSRIs to reduce alcohol use and symptoms of PTSD in a comorbid population [36,37].

- Sertraline may prolong time to relapse to cocaine [38,39].

Benzodiazepines — Use of benzodiazepines for the treatment of anxiety-related disorders in patients with comorbid SUD is controversial [40,41] due to several key considerations:

- Benzodiazepines carry abuse liability.

- There is a theoretical increased risk of diversion with this class of medications among individuals with SUD.

- Benzodiazepines also cause respiratory depression, and risk of fatal overdose is increased when taken with other alcohol/drugs. There is a fourfold increased risk of fatal overdose among patients concurrently receiving opioids and benzodiazepines [42].

- There is little evidence to suggest that benzodiazepines are more likely to be misused among individuals with other SUDs, however, and the majority of individuals with SUDs who use benzodiazepines report using them for therapeutic relief of anxiety [43,44]. An uncontrolled observation trial of lorazepam and disulfiram in 41 patients with DSM-IV alcohol dependence and an anxiety disorder found reduced anxiety levels and no evidence of benzodiazepine misuse [45].

- If benzodiazepines are prescribed in individuals with concurrent SUD, precautions should be undertaken including baseline and ongoing monitoring of substance use (eg, amount, frequency). Such precautions include providing rigorous patient education and risk-benefit decision-making prior to initiation of benzodiazepine treatment, setting clear boundaries regarding prescriptions, using state prescription drug monitoring programs to assess whether patients are receiving additional benzodiazepine prescriptions from other providers, and assessing for the development of tolerance or addictive-related behaviors which could increase risks for respiratory depression and overdose.

- In patients with a long history of benzodiazepine treatment in whom SUDs are secondarily determined, clinicians are advised to extensively counsel the patient about risks of fatal

respiratory depression when taken with alcohol and opiates.

- When benzodiazepines are to be discontinued, a slow taper is usually advisable to reduce the risk of withdrawal seizures as well as worsening anxiety, with the duration of the taper relative to the length on benzodiazepine treatment.

Gabapentin

- Gabapentin has been found to reduce alcohol craving and withdrawal symptoms in the treatment of alcohol use disorder [46].

- Gabapentin has not been systematically studied in generalized anxiety disorder. In a trial of 100 patients with symptoms of alcohol withdrawal, gabapentin reduced anxiety in patients with comorbid alcohol use disorder compared with lorazepam [47].

- A 2015 Cochrane review found no evidence to support improved abstinence rates or decrease in cocaine use frequency [48]. Gabapentin may worsen some treatment outcomes.

- While there have been a few reports of gabapentin misuse, in our clinical experience, patients infrequently request dose increases or early refills, suggestive of limited abuse liability compared with other anxiolytics such as benzodiazepines.

- Based upon case reports and human studies, the United States Food and Drug Administration issued a safety alert in 2019, warning that gabapentin may be associated with respiratory depression when administered to patients receiving central nervous system depressants or patients with underlying respiratory impairment [49]. In prescribing gabapentin to patients with these risk factors, it is prudent to start the drug at a relatively low dose (eg, 100 mg three times daily) and monitor patients for symptoms of respiratory depression (eg, unusual dizziness, dyspnea, or extreme sedation).

Other antidepressants — Tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) are less frequently utilized in clinical practice for the treatment of anxiety-related disorders due to the superior safety profile of SSRIs and SNRIs and the need to monitor tyramine consumption during MAOI treatment to prevent the development of a potentially lethal hypertensive crisis.

- While TCAs have not been widely studied in the treatment of SUDs, a clinical trial of 88 patients with PTSD and DSM-IV alcohol dependence found that desipramine was superior to paroxetine in reducing alcohol use; paroxetine led to greater reduction in PTSD symptoms [37].

- In clinical trials of imipramine for cocaine and methamphetamine use disorders, no benefit in abstinence was seen [50,51].

- Serotonin syndrome may result when TCAs or MAOIs are used in conjunction with MDMA, cocaine, amphetamines, and opioids.

- Cocaine or amphetamines may also contribute to hypertensive crisis when used in conjunction with MAOIs.

Other anxiolytics

- Buspirone is less commonly utilized for anxiety treatment in clinical practice compared with SSRIs/SNRIs due to its two to three time per day dose schedule. A clinical trial of 51 patients with alcohol use disorder and comorbid generalized anxiety disorder found greater reductions in anxiety symptoms with buspirone compared with placebo but no evidence for reduced relapse or substance [52].

- Hydroxyzine is sometimes used for its sedating effects in conjunction with anxiety disorders but has not been systematically studied for use in any SUD population.

- Mirtazapine has shown evidence of reduction in cocaine and methamphetamine use in small clinical trials [53,54].

- Prazosin has been found to reduce sleep disruption and nightmares in some studies of patients with noncomorbid PTSD [55-60] (see "Posttraumatic stress disorder in adults: Treatment overview"). Clinical trials of prazosin in patients with co-occurring PTSD and alcohol use disorder have found mixed results for drinking outcomes but no difference in PTSD or sleep outcomes.

  - A randomized clinical trial comparing prazosin versus placebo in 30 individuals with PTSD and alcohol use disorder found that prazosin led to greater reduction in percent days drinking and percent days heavy drinking compared with placebo. No difference between groups was seen in reduction of PTSD symptoms.

  - A randomized clinical trial comparing prazosin versus placebo among 96 veterans with PTSD and alcohol use disorder found no differences between groups in reduction of PTSD symptoms, alcohol use, or sleep impairment [61].

- N-acetylcysteine – A randomized clinical trial compared N-acetylcysteine versus placebo in 35 veterans with PTSD and SUD. Individuals who received N-acetylcysteine had greater

reduction in PTSD symptoms, craving, and depression compared with the placebo. Both groups evidenced significant reduction in substance use with no group differences [62].

- Topiramate – A randomized clinical trial compared topiramate with placebo in 30 military veterans with alcohol use disorder and PTSD [63]. After 12 weeks, topiramate was associated with greater reduction in alcohol use, craving, and PTSD severity compared with placebo. Hyperarousal symptoms tended to greater reduction with topiramate.

Anxiolytic properties of medications for SUDs — To date, only five medications have been FDA-approved for the treatment of SUDs: disulfiram, naltrexone, and acamprosate for alcohol use disorder, and methadone, buprenorphine, and naltrexone for opioid use disorder. Few trials of these medications have studied their effects on comorbid anxiety-related disorders. In our clinical experience, the medications can be safely used in patients with SUD and comorbid anxiety disorders.

- While acamprosate is less frequently used than naltrexone for the treatment of alcohol use disorder due to its three times a day dose schedule, an open-label uncontrolled trial with 21 patients with an anxiety disorder found acamprosate use to be associated with a reduction in anxiety symptoms [64].

- An uncontrolled clinical trial of disulfiram and lorazepam in 41 patients with alcohol use and anxiety disorders showed large reductions in both alcohol use and anxiety, although adherence to this combination therapy may be lower in nonclinical trial settings [45].

- Both naltrexone and disulfiram have been shown to be safe and effective in comorbid alcohol use disorder and PTSD [65].

- The addition of naltrexone to exposure therapy in a randomized clinical trial led to improvement in one drinking outcome, but no change in PTSD symptoms compared with exposure therapy alone [11]. The trial compared the efficacy of naltrexone (100 mg/day) plus prolonged exposure therapy, their combination, or supportive counseling among 165 individuals with PTSD and alcohol dependence. The group that received prolonged exposure therapy plus naltrexone had the lowest drinking severity at follow-up. Participants who received naltrexone had lower percent days drinking than participants who received placebo.

Medications and hepatic impairment — Hepatic impairment may occur in substance users as a result of prolonged alcohol use or as a consequence of hepatitis C infection. While mild impairment typically does not require dose adjustments, many SSRIs (with the exception of escitalopram), SNRIs, benzodiazepines, TCAs, and MAOIs should be prescribed in reduced doses

in moderate to severe liver impairment. Others, such as duloxetine and buspirone, should be avoided in severe liver impairments. Clinicians are encouraged to check liver function prior to and during the use of these medication in SUD patients.

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: Anxiety and anxiety disorders in adults" and "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".)

SUMMARY AND RECOMMENDATIONS

Anxiety-related disorders include the anxiety disorders as well as posttraumatic stress disorder and obsessive-compulsive disorder. These disorders are frequently accompanied by co-occurring alcohol and drug use disorders. Treatment choice as well as treatment outcomes for co-occurring anxiety-related disorder and substance use disorders (SUDs) are each influenced by the presence of the other disorder. (See 'Introduction' above.)

- For most patients with a co-occurring SUD and anxiety-related disorder, we suggest first-line treatment with an integrated cognitive-behavioral therapy (CBT) that addresses both disorders over other treatments (**Grade 2C**). Medication treatment with a selective serotonin reuptake inhibitor (SSRI) or a serotonin-norepinephrine reuptake inhibitor (SNRI) is a reasonable alternative in patients who prefer medication treatment or if CBT is not available. (See 'Approach to treatment' above and 'Integrated CBT' above.)

- We favor combined treatment with integrated CBT and an SSRI or SNRI rather than CBT or a serotonergic antidepressant alone in most patients with a co-occurring anxiety-related disorder and SUD in the presentations described below. (See 'Approach to treatment' above.)

    - Anxiety disorder has previously responded to treatment with a serotonergic antidepressant.

    - Anxiety disorder is severe and disabling.

- The anxiety and substance use disorders are accompanied by other comorbidities (eg, depression).
- Anxiety disorder fails to respond adequately to treatment with either modality as monotherapy.

- Components of integrated CBT for co-occurring anxiety and substance-use disorders typically include (see 'Integrated CBT' above):
  - Education and coping skills training for both disorders
  - Exposure or other behavioral interventions for the anxiety disorder
  - Relapse prevention for SUDs in patients who have achieved abstinence
- Clinical trials of integrated CBT for co-occurring anxiety-related disorders and SUDs have shown mixed results compared with treatment as usual or active interventions addressing one of the two comorbid disorders. (See 'Integrated CBT' above.)
- Medications have not been widely tested in the treatment of comorbid anxiety disorders and SUDs. (See 'Pharmacotherapy' above.)
- Of the medications used to treat anxiety-related disorders, the SSRIs, SNRIs, gabapentin, and buspirone are generally the safest medications for use in patients with SUDs. Benzodiazepines, tricyclic antidepressants, and monoamine oxidase inhibitors have the highest risks of fatalities in the comorbid population and should usually be avoided except under expert management. (See 'Pharmacotherapy' above.)
- Selection of medications for treatment of co-occurring anxiety-related disorders and substance use disorders should take into account the abuse potential of medications prescribed, as well as the potential for toxic interactions between the medications and misused substances, and between the medications and medical conditions caused by the substances. (See 'Pharmacotherapy' above.)
- There is no consistent evidence that medications used to treat SUDs worsen anxiety-related disorders. (See 'Anxiolytic properties of medications for SUDs' above.)

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