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Complex Comorbidity of Substance Use Disorders with Anxiety Disorders: Diagnosis and Treatment

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Additional information is available at the end of the chapter

Abstract

Substance use disorders is a worldwide public health problem that commonly ocur together with our psychiatric and medical disorders. Along with etiologic origins, prognosis of anxiety disorders intercepts with substance use disorders. Due to overlapping symptoms and complaints, it is always difficult for clinicians to recognise these disorders separately. In addition, selecting the best treatment approach is challenging because of the relative risk for developing anxiety disorders in substance use patients or vice versa. In this chapter, authors are focused on adding new aspects to the clinicians for evaluating, treating and following patients with comorbid substance use disorder and anxiety disorder.

Keywords: anxiety disorder, substance use disorder, comorbidity, diagnosis, treatment

1. Introduction

Comorbidity is a medical term, implying any distinct additional clinic condition that exists during the progress of an index disease in a patient. Growing evidence has revealed various associations or interactions between many mental disorders. Nevertheless, when evolving diagnostic criteria and symptom diversity are taken into account, researchers developed different definitions in order to build a consensus among clinicians for patients meeting criteria for more than one mental disorder. Several authors asserted the terms "dual diagnosis", "concurrent disorders" and "co-occurring disorders" for defining such patients, and the authors of this chapter will use the term "comorbidity" to indicate any anxiety disorder and any substance use disorder (SUD) co-observed in the same individual. Although there is insufficient data about the underlying mechanisms of psychiatric comorbidity, the presence of comorbidity is generally associated with worsened prognosis, poor treatment outcomes, medication abuse risk and lower treatment compliance.

As a statistical rule, disorders with high prevalence rates might be expected to be diagnosed in the same individual concurrently. When it comes to mental disorders, epidemiological studies in general population have detected a frequent occurrence pattern. Taken together, despite some methodological issues, anxiety disorders and substance use disorders are both disabling conditions, which often occur together.

2. Epidemiology

Data from clinical studies and community-based studies report a significant association between these disorders. In their first article derived from the results of the National Institute on Alcohol Abuse and Alcoholism's National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), Grant et al. used Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM–IV) definitions for this study and found that 12-month prevalence of any anxiety disorder was 11.08%, 12-month prevalence of any SUDs was 9.35% [1]. Among individuals with any SUDs, 17.71% had at least one independent anxiety disorder during the last 12-month period, and 1.46–10.54% had a specific anxiety disorder. Among participants with an anxiety disorders, 14.96% of them had at least one substance use disorder. Diagnosed with alcohol and drug use disorders increased the risk for any anxiety disorders 1.7–2.8 times. A few years later Grant et al. announced weighted 1-year incidence rates of any anxiety disorders and any drug use disorders, as 1.57 and 0.31, respectively [2]. In their NESARC-III study, in which they used DSM-5 criteria, they found prevalence rates of 12-month any drug use disorder as 3.9% and rates of lifetime any drug use disorder as 9.9%. Also, they announced adjusted odd ratios for the association between 12-month drug use disorder and any anxiety disorder as 1.2 and 1.3 for the association between lifetime drug use disorder and any anxiety disorder [3]. Using data from NESARC study, Conway et al. postulated that lifetime prevalence rates of any anxiety disorder among people diagnosed with drug use disorders are higher than the general population, 29.9 versus 16.16% [4]. Compton et al. used the same data and announced that after adjusting for psychiatric comorbidity, odds ratios detected statistically significant only between any anxiety disorder and drug dependence [5]. According to Mericle et al., approximately 8.2% of white Americans, 5.8% of Latin Americans, and 5.4% of Black Americans 2.1% of Asian Americans met criteria for lifetime co-occurring substance use and mental disorders. With regard to the data composed of three different community-based surveys, Mericle et al. suggested that 55.4% of individuals diagnosed with any SUDs also met criteria for any mental disorders, and among them, any anxiety disorders were the highest with a co-occurance rate of 47.3% [6].

Community-based epidemiologic studies have also been conducted in other countries. In their latest study, derived from the data from the 2007 National Survey of Mental Health and Wellbeing, McEvoy et al. found no significant relationship between any anxiety disorder and any SUD [7]. Merikangas et al. analysed six studies from Germany, Mexico, Netherlands, United States and Canada and found a strong association between anxiety disorders and SUDs. Comorbidity rates of anxiety disorders and SUDs were different among these countries and varied between 9.9 and 56% [8]. Leray et al. announced that overall prevalence of

Study	Sample	Diagnostic tools	Results
Grant et al. 2006 [1]	43,093 Americans NESARC	DSM-IV (AUDADIS)	In a 12-month period 17.71% of individuals with SUD met criteria for AD
Grant et al. [2]	34,653 Americans NESARC	DSM-IV (AUDADIS)	Weighted incidence for any AD is 1.57, for any SUD is 0.31. Low risk for comorbidity
Grant et al. [3]	36,309 Americans NESARC	DSM-5 (AUDADIS)	People with DUD are 1.2 times of greater risk of having any AD in 12-month period, 1.3 times of greater risk for lifetime
Compton et al. [5]	43,093 Americans NESARC	DSM-IV (AUDADIS)	Among all mental disorders in the study, odds ratios are only significant between any AD and drug dependence
Conway et al. [4]	43,093 Americans NESARC	DSM-IV (AUDADIS)	Prevalence of any AD is higher among individuals with DUD than the normal population, 29.9 vs 16.16%
Mericle et al. [6]	20,013 US Citizens CPES	DSM-IV (WMH-CIDI)	Prevalence rate of any AD among people with SUD is 47.3%
McEvoy et al. [7]	8841 Australians NSMHWB	DSM-IV (WMH-CIDI)	No significant association between SUD and any AD
Merikangas et al. [8]	USA, n = 2874 Germany, n = 3021 Mexico, n = 1734 Netherlands, n = 7076 Ontario, n = 6902 USA, n = 8098 ICPE	DSM-III-R	Different comorbidity rates between AD and SUD, ranging from 9.9 to 56%
Leray et al. [9]	36,105 French citizens MHGP	MINI	3.7% of people with any AD met criteria for drug addiction
Toftdahl et al. [10]	463,003 Dutch citizens	ICD-10	Prevalence rate of any SUDs in patients with AD, PTSD and OCD is 24.8, 17 and 11.4%, respectively
Lai et al. [11]	22 epidemiologic surveys	Variable diagnostic methods	People diagnosed with any SUD are of 2.9 times greater risk of diagnosing any AD

Only studies with epidemiologic surveys are included. NESARC, National Epidemiological Survey of Alcohol and Related Conditions; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; AUDADIS, National Institute on Alcohol Abuse and Alcoholism's Alcohol Use Disorder and Associated Disabilities Interview Schedule; AD, anxiety disorder; SUD, substance use disorder; DUD, drug use disorder; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; CPES, Collaborative Psychiatric Epidemiology Studies; NSMHWB, National Survey on Mental Health and Wellbeing; WMH-CIDI, World Mental Health-Composite International Diagnostic Interview; ICPE, International Consortium in Psychiatric Epidemiology; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised Form; OCD, obsessive-compulsive disorder; PTSD, posttraumatic stress disorder.

Table 1. Brief information about recent population-based studies of anxiety disorders-SUD comorbidity.

anxiety disorders in adult French population was estimated to be 21.6 and 3.7% of individuals with a diagnosis of an anxiety disorders also met criteria for drug addiction [9]. In a recent population-based study from Denmark, Toftdahl et al. established prevalence rates of SUDs in patients with anxiety disorders, posttraumatic stress disorder (PTSD) and obsessive-compulsive disorders (OCD) as 24.8, 17 and 11.4%, respectively [10]. In a recent meta-analyses and systematic review in which 22 community-based studies from different countries were evaluated, Lai et al. found high association between illicit drug use and any anxiety disorder (pooled odds ratio 2.907). In other words, people with SUDs were 2.9 times of greater risk of having any anxiety disorder [11]. **Table 1** presents the brief information about the studies aforementioned.

Epidemiologic studies focusing on clinical cases often examined prevalence of anxiety disorders (ADs) in individuals with SUD and prevalence estimates range from 4 to 80.3%. In their prospective cohort study, Franken and Hendriks detected lifetime prevalence of any AD as

Study	Sample	Diagnostic tools	Results
Franken and Hendriks [12]	116 inpatients under substance abuse treatment	CIDI SCL-90 DSM-III-R ASI-Drug	Lifetime prevalence of any AD was 53.4%, current prevalence was 38.8%
Bakken et al. [13]	146 alcohol-dependent inpatients 114 poly-substance-dependent inpatients	DSM-IV CIDI	Weighted incidence for any AD is 1.57, for any SUD is 0.31. Low risk for comorbidity
Bakken et al. [14]	60 poly-substance abusers, 194 alcohol-dependent patients	DSM-IV CIDI HSCL-25	48.6% of the sample met criteria for SAD
Sbrana et al. [15]	287 patients with various mental disorders, inpatient and outpatient setting	SCID	4% of patients with OCD also had DUD, 6% of the patients with PD also had DUD
Rosen et al. [16]	140 opiat-dependent patients over 50 years old	CIDI SF-12v2	27.8% of dependent patients also had PTSD, 29.7% of dependent patients had GAD
Smith and Book [17]	56 outpatients involved in substance abuse treatment program	SCID PSWQ ASI BDI	Prevalence rate of any AD among people with SUD is 47.3%
Goldner et al. [18]	Systematic review and meta-analysis, including 11 studies	Various diagnostic tools	29% of the patients in the studies met criteria for ADs and 50% of the participants reported anxiety symptoms

Only studies consisting of clinical samples are included. DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised Form; ASI-Drug, ASI Drug Use Severity Composite Score; CIDI, Composite International Diagnostic Interview; SCL-90, Symptom Checklist-90 Revised; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; HSCL-25, Hopkins Symptom Checklist; SAD, social anxiety disorder; SCID, Structured Clinical Interview for DSM-IV; PD, panic disorder; DUD, drug use disorder; SF-12v2, Short form health survey; PTSD, posttraumatic stress disorder; GAD, generalised anxiety disorder; ASI, anxiety sensitivity index; BDI, Beck depression Inventory; PSWQ, Penn State Worry Questionnaire.

Table 2. Brief information about recent clinical studies of anxiety disorders-SUD comorbidity.

53.4% and current prevalence of AD as 38.8% in an inpatient substance abuse population [12]. Bakken et al. asserted that current social anxiety disorder (SAD) diagnosis among patients with SUD was 51%, and this rate was higher than the alcohol-dependent patient group [13]. In their later study, Bakken et al. reported 48.6% of their study population met criteria for SAD [14]. Sbrana et al. evaluated both inpatients and outpatients diagnosed with mental disorders and found that 4% of the participants with OCD had drug use disorder, and 6% of the participants with panic disorder (PD) had drug use disorder [15]. In patients with opiate dependency, Rosen et al. found the prevalence of PTSD and generalised anxiety disorder (GAD) as 27.8 and 29.7%, respectively [16]. Smith and Book analysed 56 patients with substance use disorder and postulated that 32% of the patient group met criteria for GAD [17]. Goldner et al. made a systematic review about patients with non-medical prescription opioid users and reported that 29% of the patients in the studies had the diagnosis of AD, and 50% of the patients were reporting anxiety symptoms [18]. **Table 2** presents the brief information about these studies.

Current literature indicates a comorbidity between substance use disorders and anxiety disorders; however, while evaluating the study results, clinicians should pay attention to some important issues including study designs, population or participants included in the study, diagnostic tools or criteria used, population size. Individuals with SUD involved in the studies may be in different stages of the disorder: experiencing withdrawal symptoms or abstinent, etc. Current diagnostic instruments are insufficiently sensitive to discriminate AD symptoms or substance-related symptoms, and training of the interviewers participated in the study for the diagnostic tools might not be standardised.

3. Development and maintenance of substance use-anxiety comorbidity

Based on search results, clinical experience and expert opinions, these disorders are both in a causal and etiologic relationship in both the development and maintenance of this comorbidity. Different models have been developed in order to shed light to the comorbidity of anxiety and substance use disorders. In direct causal model, a primary psychopathology causes a secondary psychopathology. It has been well known that some substances including alcohol reduce anxiety and stress levels in a short time after they are consumed. This model is named as "tension-reduction" [19], "self-medication" [20] and "stress-response-dampening" [21] by different researchers. In all models, individuals use substances in order to reduce their anxiety levels and therefore, in most of the studies evaluating AD-SUD comorbidity, results indicate AD precedes the SUD. Smith and Book found GAD preceding to SUD in their study [17]. Having PTSD diagnosis was a risk factor for SUD, reported in a 10-year longitudinal study [22]. But also, according to the vulnerability hypothesis, any substance use increases anxiety levels and psychological arousal in time and makes the individual prone to develop PTSD after traumatic event or stress. Robinson et al. found evidence supporting self-medication theory and put forward the idea that self-medication in AD constitutes risk for developing SUD or vice versa [23]. Swendsen and Conway found that except GAD, ADs were predictors of later drug dependence [24]. In another community-based study, SAD was found to

be a risk factor for cannabis dependence [25]. On the contrary, there are studies pretending that substance-related symptoms and/or substance withdrawal symptoms might play a role in the onset of AD. Using the data from a large community sample, authors claimed that lifetime cannabis use was found to be associated with lifetime and current panic disorder (PD) diagnosis, but current cannabis use was associated with only panic attacks [26]. Brady et al. conducted a clinic study and asserted that half of the patients had PTSD before onset of cocaine dependence, and the other half met criteria for cocaine dependence before PTSD diagnosis [27]. According to Stewart and Conrod, once the comorbidity is present, these disorders pretend to serve to maintain the existence of one another. In bidirectional model, an individual with an AD may use substances in order to relieve symptoms of anxiety or stress. In time, after SUD develops, experiencing craving or withdrawal might exacerbate physical symptoms, and thus, panic attacks may be triggered or anticipation anxiety for the attacks may escalate [28].

Although epidemiological evidences are relatively determined, there is subtle data in the literature regarding biological etiology of this comorbidity. Hodgson et al. examined a sample of Mexican-Americans and identified a region on chromosome 18, possibly responsible for drug dependence and anxiety comorbidity [29].

4. Assessment and diagnosis

In the literature, assessment of comorbid mental disorders is generally performed in non-SUD psychiatric patients, and it is a bit more complicated to assess the comorbid mental disorders of patients with current diagnosis of SUD. In individuals with SUD who are applying to health care providers, it might be difficult for professionals to distinguish anxiety symptoms from the anxiety disorder. When evaluating the presenting symptoms, it is better to keep in mind that symptoms might be independent of the substance used, might be secondary to intoxication or withdrawal or might be due to an unidentified effect of the substance used. Diagnosing the comorbidity is often complicated by the anxiolytic or anxiogenic effects of the substance used. Being an extension of the primary/secondary disorder model, the DSM-IV and DSM-V classifies "substance-induced disorders (SIDs)" as a distinct diagnostic entity, which occurs during a period of heavy substance use or within the first 4 weeks of withdrawal. To diagnose a SID, symptoms should be heavier and more disabling than the symptoms expected to be presented in withdrawal or craving. A question may arise while evaluating a patient with SUD. Would diagnosing an AD in a patient with SUD require great distress and social/occupational impairment or would endorsement of the symptoms/diagnostic criteria by the patient be enough for the diagnosis?

Structured Clinical Interview for DSM-V (SCID) is a semi-structured interview tool, designed for clinicians and interviewers with adequate training and/or clinical expertise. Having four different versions (clinician, personality disorders, research and clinical trials), it is offered to be used after a short overview and general screening of the patient. Although administration of the tool can take up to several hours, test-retest study of DSM-IV diagnoses postulated excellent reliability of Axis I and Axis II diagnoses and SUDs [30]. Because established

questionnaires and scales implemented in non-abusers might misdirect both the patient and the clinician. In line with this hypothesis, Kranzler et al. conducted a research in a population with SUD and asserted that, SCID had poor validity for AD in such populations [31]. Kranzler et al. also asked the efficiency of the clinicians in diagnosing psychiatric disorders in patients with SUDs and found that clinicians using an unstructured clinical interview may be effective in diagnosing SUD, but, on the other hand, they may fail in diagnosing comorbid psychiatric disorder. They offered using SCID by trained clinicians may enhance the validity of both SUD diagnosis and comorbid disorders [32].

Thus, a more reliable and valid diagnostic tool for evaluating psychiatric disorders among substance abusers, Hasin and Grant developed the semi-structured diagnostic interview, Psychiatric Research Interview for Substance and Mental Disorders (PRISM) [33]. As well as substance use diagnosis, clinicians can use PRISM in order to evaluate current or lifetime diagnosis of some psychiatric disorders. Diagnostic sections of PRISM are modular, providing the interviewer to use it for treatment or research needs. Question patterns in the substance use module need gathering further and detailed information from the patient, if only the response is "yes" to any of them. After publication of DSM-IV, PRISM adapted to PRISM-IV, but one study found that the reliability of some DSM-IV ADs in the adapted form was lower when compared to other mental disorders [34].

Developed by the National Institute on Alcohol Abuse and Alcoholism (NIAAA), The Alcohol Use Disorder and Associated Disabilities Interview Schedule (AUDADIS) is used for diagnosing current or lifetime diagnoses of mood, anxiety, SUD and personality disorders. Although it is commonly used for population-based surveys, clinicians can use AUDADIS to tailor the treatment of the patient based on the responses to this schedule. Hasin et al. found this semi-structured interview concordant with PRISM-5 and suggested them for determining dimensional measures of psychopathology [35]. Developers of the tool recommend using computer-assisted version.

The Composite International Diagnostic Interview (CIDI), developed by World Health Organisation, helps clinicians in gathering information both for diagnosis and treatment planning. Concordance of CIDI with SCID found to be excellent for alcohol dependence, fair for drug dependence, good for alcohol and drug abuse [36].

The assessment of patients with AD and SUD comorbidity is a sensitive process, which requires a good therapeutic relationship, detailed medical history and both physical and psychiatric examination. Family history of any mental disorders should be interviewed and establishing contact with a spouse or a family member would bring contribution. Drawing a timeline representing the course of the psychiatric and physical symptoms and diagnosis would be helpful in detecting periods of exacerbation and remission.

Evaluating the patient during period of abstinence from substances is generally recommended, but it can be difficult in clinical practice. Forming a retrospective timeline showing both anxiety and substance use symptoms longitudinally might shed light into temporal sequence and the presence of anxiety symptoms during abstinence periods. Patient might create a prospective diary system by recording substance use and physical/mental symptoms. This system might help understanding which situations or emotions direct the individual to

substance use and whether withdrawal or craving can precipitate or exacerbate symptoms of anxiety. The information gathered from this diary system would also be useful for the clinician in formulating a treatment plan and later evaluation of the efficacy of the treatment interventions [37].

5. Prognosis in comorbidity

Recent evidence indicates current diagnosis of AD result in poorer treatment results and increased relapse risk in patients with SUD. In other words, patients who have anxious complaints or symptoms during or after SUD treatment might carry risks for using various substances to alleviate anxiety symptoms. As Smith and Book reported in their study, GAD interferes with SUD treatment [17]. In Oumette et al.'s follow-up study, comorbid AD impaired engagement in SUD treatment, and comorbid AD-SUD patients had worse results in functioning and symptom measures when compared with patients with SUD alone. About 41.6% of patients with comorbid diagnosis reported significant distress [38]. Ford et al. reported that severity of PTSD symptoms is associated with poor contingency management, but not standard treatment [39]. In their follow-up study, Mills et al. found no relation between PTSD and poor treatment initiation/completion of SUD. But also in this study, 2 years after the beginning of treatment, PTSD symptoms remained significant and caused disability [40]. In addition to these results, Tomasson and Vaglum found better SUD treatment outcomes with comorbid ADs [41].

Brown et al. found that in women with PTSD, relapse occurred more rapidly than non-PTSD women and the authors claimed that substance using individuals with PTSD return immediately to using substances to relieve their anxiety symptoms [42]. Brown also examined 6-month outcomes of women with PTSD-SUD diagnosis, and relapse was observed at 52% of the patients. Twenty-four percent of the population remitted from PTSD. In this study, only significant predictor of substance use relapse was the severity of PTSD re-experiencing symptoms at attendance. Re-experiencing symptoms were also identified as predictor of PTSD status at follow-up [43]. Oumette et al. evaluated male patients in their post-treatment period for 2 years and revealed that SUD-PTSD individuals had poorer treatment outcomes, and also SUD-only individuals were more likely to have remitted than SUD-PTSD group [44]. In another study by Oumette et al., they reported that attendance to the 12-Step program was associated with remission (defined as abstinence from all drugs, no problems associated with substance use and minimal alcohol use). They also emphasised that soon after discharge from acute SUD treatment, starting PTSD-oriented treatment was predictor of SUD remission 5 years later [45, 46]. Taken together, PTSD-SUD individuals tend to relapse more quickly following SUD treatment, PTSD re-experiencing symptom severity is a predictor of relapse to substance use, starting the PTSD treatment soon after SUD treatment is associated with better substance use outcomes in 5 years.

There is limited information about PD-SUD comorbidity in the literature. In a community-based study, among other mental disorders, PD had the greatest odd ratio for being diagnosed with current SUD [47]. Fals-Stewart and Schafer examined the effects of OCD diagnosis

on SUD, and among participants, those who took interventions for OCD had better treatment outcomes and had longer periods of abstinence [48]. According to Bruce et al., the presence of a SUD decreased the treatment outcomes of GAD by nearly fivefold and increased the recurrence of GAD symptoms by nearly threefold. There were no differences in treatment responses or recurrence rates for social phobia at 12 year follow-up period [49]. Differences in the results of the studies may be related to diagnostic instruments, nature of the substance used and duration of treatment administered.

In their systematic review, Fatseas et al. evaluated 12 studies available from the literature and found lifetime prevalence of anxiety disorders ranging from 26 to 35% in opiate-dependent patients under treatment. In opiate-dependent patients anxiety comorbidity had a complex and heterogeneous aetiology, but the current data recommend treating anxiety disorders in the first place in order to prevent opiate dependence. Among ADs in these studies, phobic disorders often precede the onset of opiate-dependence [50].

6. Treatment approaches

Even SUD-AD comorbidity has unfavourable outcomes, patients and families often encounter economic and systemic barriers to achieve treatment. Between 2003 and 2006, only 9–11% of those who could benefit from drug treatment could able to receive treatment [51]. In a review, current barriers to reach treatment were defined as payer financing systems, clinical and organisational limitations and confidentiality of patient records [52].

The most important part of treatment planning is deciding when (immediate or elective) and how (pharmacoterapy, psychotherapy, hospitalisation or integrated approaches) to treat these comorbid psychiatric conditions. Results from current studies present a complex aspect of the effect of the comorbidity of these disorders on treatment outcomes. The impact of AD diagnosis on SUD outcomes is complex that some studies suggest no significant impact on treatment outcomes and some suggest worse outcomes. But all of the study results agree on no clear negative effects of pharmacotherapy on anxiety outcomes. Also SUD treatment does not directly impact anxiety symptoms but in early stages of abstinence, following detoxification, anxiety symptoms significantly decrease.

Very few studies examined the safety and efficacy of pharmacotherapy for comorbid AD-SUD diagnosis. Buspirone was used in a group of opiate-dependent patients under methadone maintenance treatment, and authors did not observe any significant improvement in anxiety or substance use outcomes [53]. A series of case reports about imipramine use for the treatment of "phobic anxiety" SUD comorbidity postulated minor short-time improvements in both AD and SUD outcomes and patients who maintained the imipramine treatment for a long time had lower relapse to substance use rates [54]. On the other hand, later studies about imipramine use for cocaine and opioid dependence did not find significant benefits for the SUD-AD comorbidity, also when tolerability of selective serotonin reuptake inhibitors (SSRIs) and selective noradrenaline reuptake inhibitors (SNRIs) taken into account, they are recommended as the first-line treatment approach [55, 56].

When compared to antidepressants, benzodiazepines have the benefits of a more rapid anxiolytic effect, but their use in the treatment of SUD-AD has been controversial, due to concerns about abuse potential. In parallel with these concerns, there is a few literature examining the efficacy of safety of benzodiazepines in the treatment of AD-SUD [55]. Also, there are data in the literature suggesting that people with a personal and family history of SUDs may be more susceptible to addictive potential of benzodiazepines and thus might carry greater risk of medication abuse [56, 57]. Additionally, benzodiazepine misuse is more common in patients with SUD, especially among those with a diagnose of more sever SUD, polysubstance users and greater psychiatric comorbidity [58]. Despite all, a case series about using benzodiazepines for AD-SUD suggested that benzodiazepines were able to sustain abstinence when patients were selected carefully and monitored closely [59].

Until well-controlled studies are conducted, safety and efficacy of benzodiazepines for this population will remain unknown. Therefore, alternative therapies with better safety and efficacy profiles are recommended as the first-line therapeutic approach. Considering benzodiazepines is recommended only after these treatment options are ineffective [56, 59].

Studies have also evaluated the effect of some pharmacotherapeutic agents for comorbid AD-SUD. Topiramate, modulating principally gamma-amino butyric acid (GABA) and glutamate-mediated neurons, has been presumed as a treatment for cocaine dependence [60]. Also, there are studies suggesting topiramate as an effective treatment option in certain ADs such as SAD [61], OCD [62] and PTSD [63]. Also, studies about another GABA-ergic agent tiagabine, which has been shown to be effective in the treatment of some ADs, have conflicting results about the treatment of SUDs [64].

After reviewing general treatment considerations, authors would like to present acknowledgement about each anxiety disorder in the light of the current literature.

7. Post traumatic stress disorder

Epidemiologic studies indicate high comorbidity rates for PTSD-SUDs. The NESARC study found lifetime prevalence as 6.4 and 46.4% of people with PTSD met criteria for any SUD and 22.3% of them met criteria for substance dependence [65]. Based on the data from the Australian National Survey of Mental Health and Well-Being survey, 34.4% of individuals diagnosed with PTSD had at least one SUD, generally more than one SUD [66]. In clinical settings, when compared to patients without PTSD, patients with PTSD found to be 14 times more likely met criteria for SUD [67]. Rates of lifetime PTSD in treatment-seeking SUD populations range from 30 to 60% [68]. Studies about PTSD-SUD comorbidity indicate earlier onset of substance use, more polysubstance use, more cognitive distortions, more comorbid mental disorders, more frequent self-destructive behaviour and increased vulnerability to revictimisation [69].

Studies trying to define neurobiological mechanisms underlying this comorbidity focused on hypothalamic-pituitary-adrenal (HPA) axis and noradrenergic system. In the cerebrospinal fluid of individuals with PTSD, levels of corticotropin releasing factor (CRF) and

norepinephrine were detected higher than normal levels. Considering the role of CRF and norepinephrine as a mediator of the relationship between stress and substance seeking behaviour, future research about these might explain "self-medication of PTSD symptoms using substances" theory in some individuals [70].

Although current knowledge suggests concurrent and integrated treatment strategies for patients with comorbid PTSD-SUD, studies about medications in the treatment of this comorbidity are lacking. In a prospective observational study, opioid replacement therapy was found to be effective at reducing substance use in patients with opioid dependence and PTSD. However, patients with comorbidity received higher doses of opioid medication and attended more psychosocial treatment sessions when compared to SUD-only group [71].

N-acetylcysteine (NAC), a derivative of the dietary amino acid cysteine, is used as a mucolytic agent for pulmonary diseases and used for acetaminophen toxicity. Providing an increase in the production of glutathione, it is supposed to restore substance-related glutamatergic dysregulation, and a study has shown its modest efficacy in reducing cocaine use and craving [72]. There are randomised controlled trials exploring its efficacy versus placebo in the treatment of SUD-PTSD comorbidity.

With the recent studies, the neuropeptide oxytocin has become a favourable treatment option in many psychiatric disorders. Because oxytocin is supposed to have anxiolytic and fear-modulating effects, it becomes a promising treatment option to augment exposure-based therapies for PTSD-SUD comorbidity [73]. Furthermore, with regard to neuroimaging studies, it is postulated that oxytocin might mitigate the dysregulation of corticolimbic brain circuitry, a neurobiological mechanism underlying SUD-AD comorbidity [74]. Current literature indicates that combining oxytocin treatment with psychosocial interventions may improve the treatment outcomes of this comorbidity.

Psychosocial treatment approaches can basically divide into non-exposure-based and exposure-based treatments. Seeking Safety (SS) aims to educate patients about decreasing risky behaviours, coping with substance triggers, developing self-control skills and enhancing communication skills to build a supportive environment. Transcend is an eclectic, 12-week partial hospitalisation group program and consists of 12-step treatment programs, cognitive behavioural therapy (CBT), psychodynamic and constructivist interventions. CBT for PTSD has an 8–12 session protocol that focuses on breath training, psycho-education and coping skills (e.g. cognitive restructuring and relapse prevention). Among these treatment approaches, researchers have been studied SS most thoroughly. But, there is no evidence supporting any significant positive effects of non-exposure-based treatments in the treatment of PTSD-SUD comorbidity [75].

Exposure-based psychosocial treatment approaches include prolonged exposure and concurrent treatment of PTSD and cocaine dependence. Prolonged exposure (PE) includes psycho-education, breathing training, *in vivo* exposure and imaginal exposure. Concurrent treatment of PTSD and cocaine dependence (CTPCD) is a 16-session treatment program. In first 5 sessions patients complete coping skills training, learn PTSD-focused psycho-education and PE treatment rationale. After one session focusing on imaginal and *in vivo* exposure, coping skills treatment is continued throughout the treatment protocol. According to a systematic review

by Dam et al., exposure-based psychosocial treatment interventions might be more promising in concurrent treatment for PTSD-SUD comorbidity [75].

8. Panic disorder

Lifetime prevalence of panic disorder was 4.7%, and 12-month prevalence of panic disorder was 2.7% in United States [76]; people with lifetime SUD diagnosis were found to be 1.3 times more likely to meet criteria for panic disorder [3]. But there is no study or case report in the literature about the treatment of PD-SUD comorbidity.

9. Social anxiety disorder

According to NESARC data, prevalence rate of SAD-SUD comorbidity is 2.4% in general population [77]. Book et al. found that the presence of SAD had a significant negative effect on treatment motivation [78]. In their later study, they also postulated that there were no differences in the anxiety levels of people seeking treatment with comorbid SAD-SUD and SAD-only, but they also suggested the clinicians to be aware of the difficulties in engaging SAD-SUD patients in social communications [79]. There is only one case report about pharmacotherapeutic approach of SAD-SUD, and gabapentin was found to be effective in a patient with SAD-SUD comorbidity [80].

10. Obsessive-compulsive disorder

There is not much study in the literature about OCD-SUD comorbidity. In their study, False-Stewart and Schafer found that symptoms of OCD were subtle for the patient, and the patients might have the tendency to hide their symptoms. They also postulated integrated OCD/SUD physchotherapeutic interventions as an effective treatment approach for the comorbidity [48].

11. Generalised anxiety disorder

People with lifetime SUD diagnosis were found to be 1.3 times more likely to meet criteria for GAD [3], and the presence of GAD has a negative impact on treatment outcomes. Because GAD symptoms may be similar to the symptoms of intoxication or withdrawal, it is recommended to delay assessment of GAD until this period ends. No clinical trials of pharmacotherapuetic interventions on GAD-SUD have been conducted.

There are no data available in the literature about the comorbidity of novel psychoactive substances (synthetic cannabinoids, designer drugs, etc.) use and any anxiety disorder. Acute or chronic use of some of these substances is associated with anxiety symptoms and some people

with anxiety disorders use these substances in order to relieve their complaints. Basically, this mutual relationship might be perceived as common etiologic origins but well-designed studies about this comorbidity should be conducted in the recent future.

12. Conclusion

In the last few decades, the close relationship between SAD and SUD has been well-documented. After then, research has focused on diagnosing comorbidity and tailoring treatment for the index patients. Today, most of the patients have the opportunity to receive treatment from both mental and addiction services. Sometimes patients are directed from one clinic to the other based on the current presenting symptoms of referral.

Although patients with SUD-AD comorbidity face with increased distress, social/occupational impairment and complicated clinical course, there is limited knowledge about effective treatment approaches. Future research should focus on developing integrated psychosocial treatments and pharmacological interventions. Discovering underlying neurobiologic mechanisms may help clinicians better understand prognostic and diagnostic parameters of this pathophysiology and treatment outcomes.

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