

Anxiety and Substance Use Disorders: Co-occurrence and Clinical Issues

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Abstract The co-occurrence of substance use disorders (SUDs) and anxiety disorders has been now well established. This association is frequent and can be explained by three models: the shared vulnerability factors model, the self-medication model, and the substance-induced model. General population epidemiological studies provide strong evidence of the frequency of the association for the most used substances: tobacco, alcohol, cannabis, and to a lesser extent sedatives, opiates, and cocaine. For substances that are less commonly used in the general population, the frequency of the co-occurrence can more precisely be studied in clinical samples. We provide the most recent literature results on the association of SUDs and anxiety, and evidence for one explicative model or the other when available. For substances with sedative properties (alcohol, benzodiazepines, cannabis, opioids), both evidence for a self-medication and for a toxic effect exist. For substances with psychostimulant properties (tobacco, cocaine, and amphetamines), the literature favors the toxic hypothesis to explain the association with anxiety disorders. We give practical steps for the recognition of these dual diagnoses

and present therapeutic issues, although the strategies are rarely evidence based.

Keywords Substance use disorders · Anxiety · Epidemiology · Association

Introduction

The co-occurrence of addiction and anxiety disorders has long been neglected because addiction was thought to be restricted to antisocial and extraverted personalities. Prevalence and clinical impact of these comorbidities have been recently more recognized and studied. For the most frequent substances, like alcohol, tobacco, and cannabis, large-scale epidemiological studies in general population samples have been performed and, for some of them, prospective data are available. Thus, robust evidence on the direction of the comorbidity has been collected. For substances that are less frequently used in the general population, large-scale epidemiological studies lack the power to detect an association with anxiety disorders, except in some countries where a specific public health problem is generated by an addiction (like prescription opioids, cocaine, or stimulants). Otherwise, knowledge on the association between anxiety and substance use disorders (SUDs) can only be drawn from clinical studies among patients in care either for anxiety disorders or for SUDs. Therefore, we will review the most significant and recent literature on epidemiologic data for the prevalence of comorbid anxiety disorders and the most frequent SUDs at first (alcohol, tobacco, cannabis) and the few data available for sedatives, opioids, and stimulants, as those substances have emerged as a specific public health problem in some countries. Then, we will describe the experience from clinicians, providing information on phenomenology and therapeutic issues for each substance.

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Methods

We performed a literature search using PubMed and the gray literature with the following keywords: (Addictive disorders OR SUD) AND anxiety disorders but also with each substance and with each anxiety disorder: Panic disorder OR Agoraphobia OR Simple Phobia OR Social Phobia OR Generalized Anxiety Disorder (GAD) OR Obsessive Compulsive Disorder (OCD). We present in the first part studies that were conducted in the general population and give the most consensual odds ratio (OR). We present in the second part studies conducted on clinical samples.

Results

Part 1. Epidemiology From the General Population

Alcohol

Alcohol is the most widely used psychotropic substance in the world, with a prevalence of alcohol use as high as 80 % in most developed countries. The prevalence of alcohol use disorder (AUD) is debated, with lifetime prevalence rates ranging from 3 to 6 % in European countries and from 14 to 24 % in the USA according to similarly well-conducted epidemiological studies. The rate may be overestimated because most temporary problematic drinking meets AUD criteria [1]. That puts lifetime AUD to the prevalence of lifetime anxiety disorders [2••], which is also around 20–25 % of the general population. Thus, the co-occurrence of those equally frequent disorders could happen by chance only. But it is now strongly established that the co-occurrence of those two types of disorders is more frequent than expected if it was only by chance. ORs for the comorbidity between AUDs and anxiety are most often between 2 and 3 but can rise to 10 for the association with agoraphobia and generalized anxiety disorder (GAD) in patients defined as having alcohol dependence, even when the ORs are adjusted with other psychiatric disorders. In the recent years, the published papers are reanalyzing previous epidemiological studies, conducted in representative samples of the general population, in the USA (ECA Epidemiology Catchment Area, NCS National Comorbidity Survey, NESARC National Epidemiologic Survey in Alcohol and Related Conditions), in Europe (ZCSYA Zurich Cohorts Study of Young Adults, ESEMeD European Study of the Epidemiology of Mental Disorders, NESDA Netherlands Study of Depression and Anxiety), and in Australia (NSMHWB Australian National Survey of Mental Health and Wellbeing of Adults). Those new analyses provide interesting findings on specific risk factors that are associated with the comorbidity: younger age and early onset of both diseases, male gender, vulnerability factors (family history of alcohol

problems, family history of anxiety or mood disorder, being single, childhood trauma, sensation seeking, or low conscientiousness), and other comorbid addictions.

As the age of onset of anxiety disorders and AUD are overlapping (childhood and early adolescence), epidemiological studies that have several waves of interview are of particular interest to try to distinguish between the self-medication and the alcohol-induced hypotheses. But they find results supporting both. Among results supporting the self-medication model, it has been shown that young adolescents with excessive timidity, inhibited behavior, or already diagnosed anxiety disorder (according to most studies: GAD and social phobia; and less replicated: panic disorder, PTSD, simple phobia) have higher risk of later AUD, with ORs around 2, when compared to the rest of the general population. Over 10 years, preexisting anxiety disorders are predictive of transition from AUD to alcohol dependence (OR 3). But on the other hand, some prospective data derived from those studies support a toxic effect of alcohol, mainly when alcohol dependence criteria are chosen. Alcohol dependence is diagnosed when several social or medical complications are present and when several quit attempts have failed, which implicate an older age of onset if compared to AUD. Alcohol dependence remains a strong predictor of incident GAD, social phobia, and panic disorder (OR 2 for each disorder). Thus, the co-occurrence of anxiety disorders and AUD is well demonstrated but remains complex, with a highly prevalent association, and both a self-medication and a toxic effect are demonstrated.

Tobacco

The prevalence of lifetime tobacco smoking varies across countries between 45 and 75 %. Current tobacco smoking in adults, almost only composed of nicotine-dependent subjects, has fallen below 20 % in developed countries, with a constant decrease in the past 20 years, while it still rises in developing countries. Those subjects have a higher risk for most psychiatric disorders (OR 2–3), including schizophrenia, bipolar disorder, and depressive disorders [3]. Anxiety disorders have also been studied on that respect and were reported to be associated with moderate increase in rates of smoking (OR 1.6) and slightly higher rates of smoking cessation failure than nonanxiety control groups (OR 1.13) [4]. A recent meta-analysis on 47 studies published found that smoking and nicotine dependence are associated with panic disorder (OR 3.3) and agoraphobia (OR 3.7) when compared to non-smokers, but the results were hardly significant [5•]. Recent analysis of prospective epidemiological studies in the general population found a secondary increase of anxiety disorders (panic attacks, panic disorder, and social phobia) among current smokers, with a sex difference males (OR 6 in males and

11 in females), adding more evidence to the previously established toxic effect of smoking on anxiety disorders [6].

Cannabis

Cannabis use has increased in the past 20 years. Lifetime cannabis use was measured between 8 and 40 % in most developed countries in studies conducted more than 10 years ago [7•]. Regular surveys conducted every year in young people have shown an increase of cannabis use, but the curve flattens in the most recent years. Current cannabis use is now around 20–25 % in young age groups (15–25 years old) and decreases in older age groups to 5–8 % after 50 years of age in the USA and in European countries [8, 9]. Cross-sectional studies have demonstrated an association between anxiety disorders and heavy patterns of cannabis use, daily use or cannabis use disorders (CUD) [10•]. A meta-analysis recently reanalyzed several epidemiological studies from the general population of ten countries (USA, Canada, Switzerland, Australia, France, Colombia, New Zealand, Netherlands, Germany, and UK). This analysis added evidence that both anxiety disorders and anxiety symptoms are associated with cannabis use (OR=1.24) and cannabis use disorders (OR 1.68) in 29 studies, even if the association was weaker in those controlling for confounding factors (demographics, other substance use, and/or other psychiatric comorbidities) [11•]. In five out of six studies with a prospective design, cannabis use was associated with later onset of anxiety symptoms, while only one study favored the reverse. The most convincing prospective study was conducted in Australia. The authors found that daily cannabis use as well as cannabis dependence were associated with later onset of anxiety disorder (OR 2.5 and 2.2) [10•]. It confirms data obtained from general population samples of adults from the USA [12]. Thus, the majority of available studies conducted in the general population favor the hypothesis of a toxic effect of heavy cannabis use or cannabis dependence leading to anxiety symptoms or disorders. But the reverse is also demonstrated, with some studies favoring a self-medication hypothesis. A new analysis of the NESARC study focusing on social phobia found an OR of almost 3 for cannabis dependence and that for most comorbid patients, social phobia preceded CUD [13•]. Furthermore, the self-medication hypothesis is supported by epidemiological studies in teenagers. For example, a recent American study realized on teenagers presenting a social anxiety disorder without substance use disorder, with a 10-year follow-up, showed an OR of 6 to develop cannabis dependence [14]. Thus, for cannabis as well as for alcohol, evidence from the general population studies supports both a toxic effect and a self-medication.

Sedatives

In most developed countries, it has been stressed for the past 20 years that benzodiazepine use and prescription were

inadequately high, with prescription duration exceeding the treatment guidelines. This chronic benzodiazepine prescription is highly associated with anxiety and depressive disorders but rise many concerns, especially in the elderly: the efficacy decreases over time and prescription cessation is difficult because of rebound anxiety or withdrawal syndrome. It is also demonstrated that benzodiazepines are associated with falls in the elderly, and it is suggested that they are associated with Alzheimer disease [15•] and death [16•]. The most recently published studies found a decrease compared to previous estimates, with a prescription prevalence of 3–7 % of the general population [17]. Patients who receive chronic prescription are a vast majority (75–80 % more than 6 months or 1 year according to studies). A factor associated with the prescription constantly found across studies was female gender, and specific factors in one study or another were as follows: being widowed, separated or divorced, unemployment, and older age. Diagnoses of anxiety disorders are also found significantly associated with benzodiazepine prescription, with a special focus on panic disorder (OR=2), as well as diagnosis of depressive disorders (OR=4) [17, 18•].

Opiates

Heroin use is estimated to regard less than 0.5 % of adults. Thus, heroin dependence is not frequent enough in the general population to allow epidemiological surveys to perform association studies with anxiety disorders. But the association between anxiety disorders and pain-killer prescription and dependence receives a specific attention in the recent literature. Indeed, in the USA, dependence to prescription opioids is a major health concern because of the rise of abuse and dependence to those medications, leading to an increased rate of medical complications including deaths by overdoses. The percentage of schedule 2 opioids prescribed during medical visits has dramatically risen between the 1990s and the 2010s (OR=8), but even more in patients with clinical anxiety (OR=11) [19•]. Anxiety disorders or anxiety symptoms such as catastrophizing are constantly found significant in the analysis of factors associated with dependence to prescription opioids [20–22, 23•].

Cocaine and Stimulants

Lifetime cocaine use is variable among countries, with countries of low prevalence between 0.5 and 2 %, such as France, Germany, and the Netherlands, while other countries have higher prevalence, between 4 and 16 % (Spain, Great Britain, Mexico, or USA). The association of cocaine or stimulant dependence and anxiety disorders is well studied in general population epidemiological studies in the second group of countries. Those studies have mainly occurred in countries of most frequent cocaine use, such as the USA, Canada, and

Spain. Cocaine use was found associated with lifetime anxiety disorders with odds ratios between 1.5 and 3 [24].

Part 2. Studies Conducted in Clinical Samples

Alcohol

Comorbid anxiety disorders (panic disorder, agoraphobia, simple phobia, social phobia, generalized anxiety disorder, obsessive-compulsive disorder, and post-traumatic stress disorder) are very common in clinical samples, ranging from 5 to 30 % in samples of alcohol use disorder (AUD) patients. In samples of anxiety disorder patients, the prevalence of AUD is usually 7–10 %, but up to 50 % of patients report self-medication of anxiety symptoms with alcohol. AUD predicts worse outcomes following treatment and must be considered as a risk factor for suicide. Clinical studies provide numerous pieces of evidence for both the self-medication hypothesis with a short-term anxiolytic effect of alcohol and for a toxic effect of prolonged alcohol consumption (abuse or dependence) that increases anxiety and induces anxiety symptoms among other withdrawal symptoms. Studies have tried to define optimal therapeutic strategies in case of a dual diagnosis. There is evidence that comorbid anxiety disorder increases the prospective risk for relapse to drinking after alcoholism treatment. Nevertheless, it is disappointing to notice that specific anxiety treatment (pharmacological and CBT) has no significant effect on the outcome of alcohol treatment programs. But there are estimations that treating the comorbid anxiety disorder can potentially prevent 40 % of transitions from abuse to dependence [25••].

Tobacco

Clinical studies have demonstrated that anxiety disorders are associated with higher levels of withdrawal symptoms, lower treatment response rate, and lower quit rate among smokers [26•].

The recent clinical literature has tried to develop explanations for the relationships between smoking behavior, nicotine dependence, and anxiety disorders. For the toxic effect, already demonstrated in previous clinical studies, some authors advocate a direct effect to the respiratory and autonomic systems that may alter peripheral and central responses to stress [27•]. But others present a model of shared vulnerability factors that increase the likelihood of smoking and of anxiety disorder development [28]. Finally, other authors advocate that patients use cigarettes as an anxiolytic self-medication [29•]. In case of a dual diagnosis, both disorders should be addressed at the same time, using validated therapeutic strategies (pharmacological and psychotherapeutic) [30, 31•]. CBT aimed at reducing the sensitivity and attention paid to physical anxiety symptoms during nicotine withdrawal has been tested. They seem effective on anxiety symptoms but their efficacy for abstinence maintenance is poorly documented [32•].

Cannabis

In clinical samples of CUD patients, a dual diagnosis with anxiety disorders is common around 50 % in the last 12 months [33], most frequently social anxiety disorder, GAD, panic disorder, and OCD.

The psychoactive effects of the cannabis consumption are multiple. The positive effects most frequently reported by subjects are relaxation, sensation of joy, well-being or even euphoria, disrupted sensory perceptions, and increased appetite. The less frequent negative effects may include anxiety, especially in naïve users or when high doses are used. The chronic use is mainly associated with cognitive deficits and lack of motivation. Withdrawal symptoms including anxiety symptoms appear 1–2 days after cessation in dependent smokers. They are at their maximum in the first week and more often disappear after 2 weeks but can persist well beyond. Other symptoms may include aggressiveness, decrease of appetite or even a loss of weight, irritability, restlessness, and sleeping disorders. This is why both short-term self-medication and long-term toxic effect are both described as explaining the comorbidity. For treatment, motivational psychotherapies and CBT have proven efficacious on cannabis cessation and abstinence. Concerning the pharmacological treatments, few studies have demonstrated an efficacy, but some authors use medications with hypnotic and anxiolytic properties such as mirtazapine for withdrawal symptoms [34]. Recent studies investigating replacement therapies cannabidiol, nabiximols, or dronabinol usually try to demonstrate an efficacy on anxiety reduction among other symptoms of withdrawal [35, 36], but the level of evidence is weak, and such studies exclude patients with severe anxiety disorders.

Sedatives

Long-term benzodiazepine prescription in the clinical management of anxiety disorders is still frequent, despite clinical guidelines that do not recommend their use for more than a few weeks. This is driven by both physicians and patients, especially if they are anxious. Indeed, benzodiazepines have a rapid efficacy on anxiety symptoms in naïve patients. They seem during the “honeymoon” like the perfect treatment when compared to antidepressants or gabapentin that needs several weeks to reach a moderate efficacy and may have side effects. But after some weeks, benzodiazepine drugs lose their efficacy because of a tolerance phenomenon, leading to a risk of dose escalation, abuse or dependence, and withdrawal symptoms.

At first sight, benzodiazepines are prescribed if an anxiety disorder or at least anxiety symptoms require medication, favoring the self-medication hypothesis. Benzodiazepine dependence should then only be secondary to a preexisting anxiety disorder. Indeed, there is to our knowledge no study assessing prospectively the occurrence of secondary anxiety disorders after chronic

“recreational” benzodiazepine use or dependence. Nevertheless, as in alcohol dependence, patients with benzodiazepine dependence may experience anxiety symptoms or panic attacks during withdrawal. The repetition of panic attacks during unprepared withdrawals may lead to the occurrence of a secondary panic disorder that will in return reinforce the need for benzodiazepines and maintain dependence, which can define a toxic effect.

In clinical samples of patients with benzodiazepine prescription, the majority lasting for 6 months or 1 year, the prevalence of current anxiety is more than 50 % (GAD, panic disorder, and depressive episode). The majority of patients meet the criteria for benzodiazepine dependence.

Therapeutic issues include of course prevention. Benzodiazepine prescription in the case of an anxiety disorder should be reduced as much as possible. Facing a patient with the dual diagnosis of an anxiety disorder and a benzodiazepine dependence, treatment should favor intensive combined approaches associating psychotherapeutic strategies to cope with anxiety symptoms, long-term pharmacological ISRS treatment for the anxiety disorder, and slow progressive tapering of the benzodiazepine prescribed. The tapering aim is usually cessation, but in the most severe and long-lasting clinical cases, a maintenance treatment with the smallest benzodiazepine dose and the longest half-life acceptable for the patient is recommended as a second-line treatment. Furthermore, there is no demonstrated efficacy for strategies such as inpatient withdrawal or anticonvulsant add-on in the case of a dual diagnosis of anxiety disorder and benzodiazepine dependence. Clinical studies assessing the efficacy of tapering strategies, despite psychotherapy add-on, are often disappointing [37•].

Opiates

The clinical diagnosis of an anxiety disorder is not easily made during periods of active heroin use because heroin withdrawal symptoms contain anxiety symptoms among pain, chills, irritability, vomiting/diarrhea, insomnia, and craving for heroin. Complete clinical interviews are more easily made in patients under maintenance treatment such as HD buprenorphine or methadone, or in heroin-assisted programs available in some countries. When it is done, between 8 and 35 % of opioid-dependent subjects can be diagnosed with lifetime anxiety disorders [38]. PTSD receives a special attention in the recent literature. One study found significant associations between PTSD and heroin addiction severity, as well as with methadone doses required [39], suggesting a self-medication effect. Dependence to prescribed painkillers is also specifically studied in American war veterans who may have at the same time combat exposure PTSD and pains that require pharmacological treatment. In those studies, a diagnosis of PTSD or its severity appears as a risk factor of prolonged pain, of opioid use, and of opioid dependence [40–43]. But on the other hand, a toxic effect of chronic heroin use leading to secondary anxiety disorder is also observed. The

NESARC study has found a risk to secondary develop panic disorder or GAD in patients with opiate or prescription opioid dependence (OR respectively 8 and 3) [23•]. Therapeutic recommendations usually involve specific CBT and pharmacological treatment of anxiety disorders combined with opioid maintenance treatment, but clinical studies are rare.

Cocaine and Psychostimulants

The acute effects of cocaine or stimulant include euphoria, tachypsychia, and grandiosity. They are also often accompanied by transient psychotic symptoms such as paranoid ideations, hallucinations, and delusions, especially at high doses or with rapid routes of administration (such as intravenous or smoked). Repetitive, stereotyped, or OCD-like symptoms are described [44, 45] during the peak effects. The few hours after the disappearance of the “high” effect, known as “the low,” are often associated with physical symptoms such as tachycardia, insomnia, restlessness, and anxiety symptoms. Those symptoms can reach the threshold of a panic attack. With repetitive use, panic attacks occurring during the “low” can become an autonomous panic disorder that may evolve independently of further cocaine use. In cocaine-dependent subjects, withdrawal included anxiety symptoms and sometimes triggers anxiety disorders that may last for as long as 1 year after cocaine or stimulant cessation [46].

In clinical samples of patients in care for cocaine dependence, the proportion of those diagnosed with current anxiety disorders has been usually found around 10 % for PTSD, 15 % for social phobia, and up to 40 % if lifetime diagnosis is taken into account. PTSD is specially associated with poor outcome after treatment [47•].

There are more prospective clinical studies showing evidence that the association between anxiety disorders and cocaine is explained by a toxic effect of cocaine that favors the occurrence of secondary anxiety disorder than studies favoring a self-medication hypothesis. Prolonged cocaine abstinence is also described as leading to a disappearance of PTSD symptoms as well as other anxiety disorders in cocaine-dependent patients with concurrent anxiety. Recent years’ literature has put a special focus on anxiety symptoms or anxiety disorders associated with emerging new stimulants, as their use spreads. This may include stimulants such as methamphetamine and cathinones, methylone, and mephedrone, the so-called “bath salts.” In clinical samples, the proportion of patients with concurrent anxiety disorders is comparable to that described several years ago in patients with crack or cocaine use disorder, between 15 and 40 % according to the sample. Interestingly, those studies came not only from the USA but also from teams working in emerging countries such as South Africa, Malaysia, Thailand, or China. Specific pharmacological trials in case of a dual diagnosis of anxiety disorders and cocaine dependence are old and use tricyclic antidepressants such as desipramine. CBT aimed at anxiety symptoms, especially PTSD, has been shown effective on the

anxiety disorder itself as well as retention in cocaine treatment programs in case of a dual diagnosis. Reduction of cocaine use was shown to be a mediator in contingency management efficacy on social phobia in patients with this dual diagnosis.

Conclusion

The association between anxiety disorders and SUD is now well established. Epidemiological studies from the general population have demonstrated a high rate of association with AUD, tobacco smoking, cannabis UD, sedative dependence, prescription opioids, and cocaine UD. Studies conducted in clinical samples allow a deeper investigation on the direction of the co-occurrence. Alcohol, like cannabis, benzodiazepines, and opiates, all of them sedative compounds, is at the same time a self-medication and a cause of anxiety disorders. There are more pieces of evidence that tobacco smoking and cocaine, both stimulants, provoke anxiety disorders, especially panic disorder. Whatever their direction, those dual diagnoses have bad prognoses and are poorly responsive to usual treatments. Nevertheless, few clinical studies address therapeutic issues: the usual guidelines recommend an intensive care combining strategies that have been validated in each disorder separately. A lot of pragmatic research with innovative tools is still needed for those challenging patients.

Compliance with Ethics Guidelines

Conflict of Interest Gaël Dupuy and Vanessa Bloch declare that they have no conflict of interest.

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