Alcohol Use Disorders and Panic Disorder: A Review of the Evidence of a Direct Relationship

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Objective: It is generally agreed that alcohol use disorders and panic disorder with (PD[A]) or without agoraphobia (PD) tend to occur within the same individual. However, the cause of this comorbidity remains controversial. Three main explanations are that (1) PD(A) promotes pathologic alcohol use as self-medication, (2) chronic alcohol use and alcohol withdrawal induce changes in the neurochemical system that promote panic, and (3) a third factor, such as familial transmission, promotes both conditions. The aim of this review was to survey the literature in order to determine the validity of these explanatory models.

Data Sources: A review of epidemiologic, family, and laboratory studies was performed. Studies were identified using PubMed (English-language articles published from 1960 to 2006, using the search term *alcohol and panic*).

Study Selection: Twenty studies were reviewed and selected according to the following criteria: PD(A) and alcohol abuse/dependence diagnosed according to the DSM, no additional comorbidity, use of adult samples, comparison with a nonclinical control group, or application of a crossover design.

Data Extraction: Nonsignificant results or trends only were reported as "no difference." Data on "anxiety disorders" or "substance abuse" in general were not included.

Data Synthesis: In PD(A), alcohol lessens anxious apprehension, thereby decreasing the likelihood of panic. In alcohol use disorders, alcohol increases CO_2 sensitivity and may thereby promote panic. In both cases, a significant familial transmission contributes to the co-occurrence.

Conclusion: Findings would seem to indicate that PD(A) and alcohol use disorders can both serve to initiate the other via independent mechanisms. Further studies are warranted.

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Substances like cocaine, marijuana, and alcohol may precipitate anxiety and, more specifically, panic.[1–3] As far as alcohol is concerned, accumulating evidence supports the view that there is a close link between panic disorder with (PD[A]) or without agoraphobia (PD) and alcohol abuse or dependence. In fact, some studies[4] show that subjects with PD(A) have a higher than expected prevalence of alcohol use disorders; other studies show that alcoholics have a higher than expected prevalence of panic.

One explanation for the etiology of such a comorbidity is that PD(A) directly promotes alcohol use disorders. The hypothesis that expresses this general view has been referred to as the "self-medication hypothesis"[5] and suggests that alcohol may decrease aversive panic-like symptoms, thereby promoting persistent and escalating use via negative reinforcement. This view has been most often supported by anxiety researchers, who tend to consider alcohol use disorders as a complication of PD(A).

In contrast, alcoholism researchers consider panic symptoms to be a consequence of chronic alcohol use, especially in cases of strong dependence or withdrawal syndrome. According to this latter view, changes in neurochemical systems induced by alcohol use or alcohol withdrawal may be responsible for the onset of PD(A).[6] In this regard, it is worth noting that researchers' backgrounds may shift the point of view from which the phenomenon is studied and influence the observation itself.

There is an alternative hypothesis that, rather than there being a direct causal relationship, both comorbid conditions may be promoted by a third factor. On the basis of the strong familial component observed in PD(A) and alcoholism, some authors have suggested that this third causal factor may run in the family.[7]

Finally, the illusion of a relationship between PD(A) and alcoholism may be due to an overrepresentation of patients with both disorders according to Berkson's bias. However, this applies only to clinical studies and not to the ones conducted in community samples.

The present article briefly reviews the existing data on the comorbidity between alcoholism and panic and focuses on epidemiologic surveys, family studies, and experimental research. The aim is to get a broader perspective on the relationship between PD(A) and alcohol abuse/dependence and to identify the possible underlying etiologic mechanisms.

METHOD

A computerized search was carried out (PubMed from 1960 to 2006) using the search term *alcohol and panic*. In addition, the reference lists from existing reviews and from the articles retrieved were inspected. Only English-language articles published in peer-reviewed journals were included.

Drawing conclusions on the basis of the results of poorly designed studies is of questionable value. To proceed in the most conservative fashion, only studies performed according to specific criteria were included in the review. The diagnosis of PD with (PD[A]) or without agoraphobia (PD) and alcohol abuse/dependence had to be made according to the *Diagnostic and Statistical Manual of Mental Disorders*. Moreover, no additional comorbid psychiatric disorders were allowed to be present at the time of participation in the study, and the study had to include adult samples. Except in the case of epidemiologic surveys conducted in the general population, a nonclinical control group or a crossover design was required.

In order to work with an approach as conservative as possible, nonsignificant results or trends only were reported as "no difference." Also, studies were excluded when the data referred to "anxiety disorders" or "substance abuse" in general and when the comorbid disorders were not specifically limited to PD(A) and alcohol use disorders.

RESULTS

Twenty articles met our inclusion criteria. What follows is, first, an overview of studies estimating the prevalence of comorbidity in epidemiologic studies in the general population, on the one hand, and in clinical samples, on the other hand. Then, the family studies looking at psychopathology in the families of probands with 1 of the 2 disorders will be reviewed. Finally, experimental studies analyzing the interaction between panic and alcohol, using panic provocation in the laboratory, will be considered.

Studies on the Prevalence of Comorbidity

In 1998, Swendsen et al.[8] aggregated and weighted the data of 4 major epidemiologic surveys and showed the lifetime risk of PD(A) for patients with alcohol abuse/dependence compared with that of non–alcohol abuse/dependence samples (i.e., odds ratio [OR]) after accounting for age, gender, and education. The OR was 3.82 (95% CI = 3.75 to 3.90) in the Epidemiologic Catchment Area (ECA) survey,[9] 2.09 (95% CI = 1.41 to 3.10) in the National Comorbidity Survey (NCS),[10] 0.97 (95% CI = 0.41 to 2.58) in the Puerto Rico study,[11] and 1.96 (95% CI = 0.93 to 4.13) in the Zurich study.[12] The ORs of having alcohol abuse/dependence comorbid with PD over the past 12 months were 4.06 (95% CI = 3.90 to 4.22) in the ECA, 1.21 (95% CI = 0.77 to 1.90) in the NCS, 0.40 (95% CI = 0.49 to 12.68) in the Puerto Rico study, and 4.08 (95% CI = 0.79 to 21.18) in the Zurich study.

In Edmonton (Alberta, Canada), a random sample of 3258 adult household residents was interviewed. The OR of alcohol abuse/dependence in those with PD(A) compared with all other subjects was 3.1.[4] Lifetime comorbidity was also measured in the Ontario, Canada population aged 15 to 64 years by means of a survey of a representative household sample. The OR of PD in the case of alcohol dependence was 2.2 (95% CI = 1.1 to 14.3).[13]

Finally, in the National Survey of Mental Health and Well-Being, a cross-sectional survey of 10,641 Australian adults, the OR (95% CI) for the association between alcohol abuse/dependence and panic was 3.9 (2.3 to 6.7).[14]

In sum, according to the results of the literature, the risk of PD(A) in cases of alcohol abuse/dependence is between 2 and 4 times higher than in cases of no alcohol abuse/dependence, the only exception being in the Puerto Rico study.[11] This exception may be due to some characteristics of the study and of the Puerto Rican population: (1) subjects over age 64 years were not included, thus reducing the possibility of seeing a lifetime prevalence rate increase due to age; (2) subjects had a low socioeconomic status, as Puerto Rico is part of the developing and third-world countries; (3) least-educated inhabitants and those living in urban areas were underrepresented, since they had higher rates of disorders for several diagnoses; thus, the overall rate of psychiatric disorder on the island may be slightly higher than what was reported; (4) Puerto Ricans may have different cultures and customs regarding disclosure of psychopathology and alcohol consumption; and (5) in Puerto Rico, a translated and adapted version of the Diagnostic Interview Schedule (DIS) was used. The interview was changed as what concerns the computer algorithms and modified, adding items according to diagnostic or cultural considerations. Moreover, fewer schedules were included because the survey was conducted by the Ministry of Health, and in this context, the full DIS appeared likely to lead to respondent fatigue. Finally, the

authors suggested that Puerto Ricans may have singular coping styles or social support networks that protect them from mental disorders.

Some epidemiologic studies also examined the temporal relationship between panic and alcohol use/dependence, which is a relevant element in clarifying the etiologic mechanisms of such a comorbidity. Krystal et al.[15] used data from the first wave of interviews from 5 communities of the ECA project to examine the comorbidity of alcohol use and panic in relation to age. Alcoholism was negatively associated with age ($p < .01$). Among men, panic disorder declined to 0/100 by age 54 for individuals reporting recent alcohol abuse and by age 45 for individuals with a past, but not recent, alcoholism history (no alcohol abuse for greater than 6 months). Among women, PD rates declined to 0/100 by age 64 for individuals reporting recent alcohol abuse and by age 55 for women with a past, but not recent, alcoholism history. Thus, PD prevalence declined earlier in subjects with a past history of alcoholism than in subjects with a recent history of alcoholism. However, when the order of onset of reported symptoms of panic and alcoholism was examined among those who met criteria for both disorders at some point in their lives, 60% had symptoms of alcoholism at least 1 year earlier than symptoms of panic, 6% reported the onset of both symptoms within the same year, and 33% reported symptoms of panic at least 1 year earlier than those of alcoholism. Although the onset of alcohol abuse or dependence was almost twice as likely to occur prior to the onset of PD, this did not reach statistical significance ($p = .11$).

Finally, according to Swendsen et al.,[8] alcohol abuse/dependence occurred prior to the onset of PD in 44.5% of subjects in the ECA, in 32.7% of those in the NCS, and in 50.0% of those in the Puerto Rico study. On the other hand, PD(A) was prior to alcohol abuse/dependence in 45.2%, 62.3%, and 33.3% of cases, respectively. The overall impression is that the temporal relationship between panic and alcohol use/dependence is still a matter of debate, with the literature showing quite heterogeneous results.

In recent decades, various publications have investigated the comorbidity of PD(A) and alcohol abuse/dependence in clinical samples. Some have addressed PD(A) subjects, and others have addressed alcoholic samples. Unfortunately, the large majority of those studies did not include a healthy control group or did not use DSM diagnostic criteria. Consequently, we reviewed only a small part of the literature.

Pollard et al.[16] compared 79 patients with alcohol dependence with 70 hospital employees and found that 10% versus 0%, respectively, had a diagnosis of PD and that 22% versus 7% had a diagnosis of PD(A). Schuckit et al.[17] evaluated 2713 alcohol-dependent subjects and 919 controls and found that 4.2% of alcoholics had PD versus 1% of controls ($p < .001$). More recently, Sbrana et al.[18] evaluated 50 consecutive PD(A) inpatients and outpatients presenting for treatment at their clinic and 50 healthy controls. They found that 4% ($N = 2$) of the PD(A) patients and 6% ($N = 3$) of the controls had an alcohol use disorder. In all cases, the rate of co-occurrence was surprisingly low when compared with that found in epidemiologic surveys. However, before concluding that clinical samples may not be representative of the general population, additional methodologically sound research should be conducted and taken into account, especially considering that the rates of PD(A) documented in uncontrolled samples of alcohol-dependent patients seeking treatment are between 13% and 25% according to the studies.[19,20]

There is also interesting literature on treatment of panic among alcohol-dependent patients. This topic has high interest today for several reasons. First, baseline comorbid panic disorder has been shown to be, among anxiety disorders, the single best predictor of a relapse to alcohol dependence after treatment.[21] Second, it would be important to clarify if a specific antipanic treatment should be postponed to 3 to 6 months of sobriety, as suggested by clinical guidelines in the 1990s[22]; proposed as early treatment of panic in alcoholics; or integrated into the standard treatment for alcoholism. Besides representing an important future research direction, the studies on this topic are to our knowledge still a small number and do not always include controls. Up to now, favorable results have been observed with administration of imipramine to depressed PD alcoholics in an open-label trial[23] and clonazepam to 3 alcoholics in a case series.[24] According to these results, early pharmacotherapy for panic in alcoholics may be indicated.

Nonpharmacologic interventions showed controversial results. Bowen et al.[25] administered the regular alcoholism program with or without cognitive-behavioral treatment (CBT) specific for panic to alcoholic inpatients with PD(A) according to a case-control design. No statistically significant differences were found between the 2 programs. On the other hand, Kushner et al.[26] reviewed the conduct and preliminary findings of a clinical trial of an integrated CBT program for alcoholism treatment patients with comorbid panic disorder. The data overviewed indicated that this program was effective in reducing panic attacks and, more importantly, serious alcohol relapses following treatment.

In brief, treatment research on panic and alcoholism is growing but still apparently not exhaustive to solve the clinical practice dilemma of which serial or integrated comorbidity treatment approach to use.

Family Studies

Since the 1980s, several studies have investigated the possibility of genetic liability or clustering in families of PD(A) and alcohol abuse/dependence. Some studies have

shown that family members of individuals with PD(A) are at an increased risk of alcoholism; others have found that family members of individuals with alcohol abuse/dependence are at an increased risk of panic.

Crowe et al.[27] collected data on 278 first-degree relatives of 41 probands with PD and on 262 relatives of 41 control probands. The morbidity risk for alcoholism was 6.1% in the first group and 3.8% in the second. Similar results were found by Noyes et al.,[28] who observed that 6.6% of PD relatives and 4.4% of control relatives had a diagnosis of alcohol abuse/dependence ($p = .01$). Once again, Goodwin et al.[29] compared rates of alcohol use disorders in the relatives of 3 proband groups (PD with lifetime alcohol use disorders, PD without lifetime alcohol use disorders, and not-ill controls). They found a significantly higher rate (12%) of alcohol use disorders among the relatives of PD probands compared with relatives of controls (5%), and anxiety symptoms were more frequent among the male relatives of panic probands who received an alcohol diagnosis compared with those who did not have alcohol use disorders.

In contrast, Merikangas et al.[7] evaluated 42 alcoholic probands and 61 controls and found an OR for having PD of 2.7 (95% CI = 1.2 to 5.8) when comparing relatives of alcoholic probands to relatives of controls. Similarly, Nurnberger et al.[30] conducted a study on a large sample of 8296 relatives of alcoholic probands and of 1654 controls, finding a relative risk of 2.15 (95% CI = 1.31 to 3.52). Adjusting for sex, ethnicity, ascertainment site, cohort effect, and comorbidity, the relative risk decreased to 1.90 (95% CI = 1.03 to 3.51).

Two additional studies should be noted as they refer to adult offspring of alcoholics. Mathew et al.[31] observed 408 adult children of alcoholics and 1477 controls and found that 2.7% and 0.7%, respectively, had a diagnosis of PD ($p < .001$) with an OR of 4.06 ($p \leq .01$). Bidaut-Russell et al.[32] studied 74 adult offspring of mothers clinically diagnosed with alcoholism and 978 control subjects. They observed in male offspring of alcoholic mothers a more than 2-fold increased risk of panic occurrence when compared with male offspring of controls (OR = 2.86, 95% CI = 0.31 to 26.52). Thus, the risk of 1 of the 2 disorders occurring in first-degree relatives of patients is almost doubled when compared with that of first-degree relatives of controls. The elevated risk of panic in relatives of alcoholics, and vice versa, seems to be confirmed also by studies on offspring.

However, family datasets also should be examined according to the pattern of co-occurrence. It might be worth clarifying if panic disorder and alcoholism co-occur in same families as an apparent phenotype (i.e., probands with PD[A] and alcoholism have relatives with PD[A] and alcoholism) or if the disorders tend to co-occur in isolation in relatives. The latter would suggest alternative phenotypic expressions of the same underlying vulnerability. This sort of analysis has already been used to make inferences about the relationship between depression and alcoholism in family studies. Moreover, this may be a starting point to strengthen the research on co-aggregation of multiple disorders as suggested by Nurnberger et al.[30] They found that rates of specific substance dependence were markedly increased in relatives of alcohol-dependent probands for cocaine, marijuana, opiates, sedatives, stimulants, and tobacco. Aggregation was also seen for panic disorder, obsessive-compulsive disorder, posttraumatic stress disorder, and major depression. These data suggest that new phenotypes for molecular genetic studies may exist, as well as alternative strategies for studying the heterogeneity of alcohol dependence.

Experimental Studies

Epidemiologic and family studies highlight the possibility of a significant causal relationship between panic and alcohol abuse/dependence. Most studies suggest that panic may promote alcohol use disorders, while other studies show that heavy drinking may induce the onset or worsening of panic. This suggests a potential complex causal link that needs to be clarified.

Experimental research may contribute to our understanding of this link, as panic attacks, the core phenomenon of PD(A), are reproduced under controlled laboratory conditions by the administration of provocative agents (i.e., sodium lactate, carbon dioxide, cholecystokinin, yohimbine, etc.). These challenges also allow the direct observation of the effects of alcohol use on the panic-like response to a provocative agent.

Lactate infusion and CO_2 inhalation are the challenges specifically used in studying the comorbidity between PD(A) and alcohol use disorders. George et al.[33] administered lactate to abstinent alcoholic patients with PD, nonalcoholics with PD, and control subjects. They found that alcoholic patients had fewer panic attacks in response to lactate infusion than nonalcoholic patients ($p < .05$), with no differences in baseline anxiety. The authors suggested that the pathophysiology of PD(A) in alcoholics is different from that in nonalcoholics. It may be argued that even past alcohol use can protect against panic attacks or at least that alcoholics with PD are resistant to CO_2.

On the other hand, Cowley et al.[34] studied the response to sodium lactate infusion in alcoholics with a history of panic attacks, alcoholics without a history of panic attacks, and nonalcoholics with PD. The rate of lactate-induced panic was significantly higher in alcoholics with panic attacks than in alcoholics without panic attacks ($p < .02$). Nonalcoholic patients with PD(A) and alcoholics with panic attacks did not differ significantly in their lactate response. The authors suggested that panic attacks in alcoholics resemble those in nonalcoholics.[34]

Kushner et al.[35] tested the acute effect of alcohol on panic symptoms by administering either alcohol or placebo to subjects with PD and then administering a 35% CO_2 challenge. State anxiety scores were significantly lower in the alcohol group at both the prechallenge and postchallenge assessment ($p < .01$ and $p < .05$, respectively). Subjects in the placebo group showed a greater increase over baseline on the postchallenge Acute Panic Inventory score than did subjects in the alcohol group ($p < .01$). No difference was found with regard to the number of panic attacks, although they occurred in 50% of the subjects in the placebo group and in 25% of the subjects in the alcohol group ($p = .15$). The authors concluded that alcohol may attenuate panicky responses in patients with PD, perhaps by acting upon γ-aminobutyric acid (GABA) receptors.[35] These results seem to contradict the previous ones obtained using lactate infusion as a challenge.[33] In reality, studies with lactate on the one hand and the ones with CO_2 on the other address different questions and do not really contradict. The first[33,34] evaluate "panicogen in alcoholics," and the second[35] are about "panicogen and alcohol administration." Thus, the first evaluate the acute effect of a panicogen agent in subjects chronically exposed or not exposed to alcohol. The second evaluate the acute effects of panicogen plus alcohol or placebo in subjects chronically exposed to panic. Considering that lactate infusion and CO_2 challenge have comparable efficacy in inducing panic under controlled laboratory conditions,[36] different previous chronic exposures may imply a different sensitivity to the panicogenic agent. For this reason, studies with lactate infusion and studies with CO_2 inhalation should be considered complementary.

Lehman et al.[37] examined the effects of alcohol outcome expectancy, subjective anxiety, and anticipatory anxiety on panic symptoms induced by a 35% CO_2 challenge in PD(A) patients after consuming either an alcoholic or placebo beverage. Participants with greater positive alcohol expectancies reported fewer panic symptoms, participants who drank alcohol reported less anxiety after the challenge, and individuals with greater anticipatory anxiety reported greater postchallenge anxiety. The authors concluded that anticipatory anxiety mediates the relationship between alcohol use and self-reported anxiety, as alcohol lessens anxious apprehension, possibly decreasing the likelihood of having a panic attack.

More recently, Rassovsky et al.[38] compared 22 detoxified, alcohol-dependent individuals with 32 healthy controls on 2 biological challenges (a breath-holding challenge and the 5% CO_2 rebreathing challenge). The alcoholic group had significantly higher CO_2 sensitivity than controls in response to both challenges, while no differences were found in the number of laboratory-induced panic attacks. The authors concluded that alcohol withdrawal may lead to CO_2 hypersensitivity and that this could be an important causal factor for comorbidity between alcohol abuse/dependence and panic. A proposed explanation is that CO_2 hypersensitivity, resulting from chronic suppression of medullary chemoreceptors by alcohol, may lead to hyperventilation during the alcohol withdrawal syndrome and that this, in turn, may promote the onset and maintenance of panic. Alternatively, acute alcohol withdrawal could lead to a pathologically dysregulated CO_2 chemosensory state, and CO_2 hypersensitivity could thus generate false suffocation alarms and trigger panic attacks, according to Klein's[39] theory.

DISCUSSION

Perhaps the strongest conclusion that can be drawn from this review is that both PD(A) and alcohol use disorders appear to have the capacity to serve as a causal factor/facilitator in the development of the other. Epidemiologic studies show a direct relationship between PD(A) and alcohol abuse/dependence. The lifetime risk of PD(A) occurrence in alcoholics ranges from 4.08 in the Zurich study to 1.21 in the NCS (United States), with the Puerto Rico study being the only exception (OR = 0.97).

As for the temporal pattern, panic onset occurs prior to alcohol abuse/dependence more frequently than the opposite pattern.[8,15] Yet, these 2 studies are the only ones suggesting this sequence pattern. The temporal pattern becomes even more complex if we consider that a past history of alcoholism has been found to be associated with an earlier decline in PD(A) prevalence compared with a recent history of alcoholism. Theoretically, this phenomenon may be differently explained. First, a successful self-medication can be considered. As an alternative, a biological degenerative process triggered by age, alcohol neurotoxicity, or alcohol withdrawal damage could be hypothesized. A natural age-related decline in panic prevalence and incidence in later life may be yet another explanation.[40] Finally, it could merely be a matter of underreporting of symptoms by elderly subjects. The first explanation seems to be an argument in favor of the self-medication theory. In the second case, the hypothesis that alcohol triggers panic would be supported. In the third case, an independent factor, like the natural history of panic, would be the explanation. In the latter case, it would be a matter of methodological biases. Clinical studies further support a direct relationship between the 2 disorders but do not suggest an order of causality.[16–18]

There is a clear familial aggregation between panic and alcohol use disorders since both occur in first-degree relatives. However, the situation in offspring is not as clear. We were unable to find studies that met our criteria in offspring of PD(A) patients. In offspring of alcoholics, 1 study[31] found a higher risk of PD, but the other[32] found this only in males.

Experimental research provides more substantial insight. Although lactate research is somewhat contradictory,[33,34] studies using CO_2 challenge have yielded crucial results. These studies suggest that alcohol does not directly influence the likelihood of panic attack.[35,37] Rather, in PD(A) patients, it seems to decrease the level of anticipatory anxiety.[35,37] In alcoholics, however, it appears to increase the CO_2 sensitivity.[38] The effect of alcohol in the 2 subpopulations would, therefore, appear to be opposite. In PD patients, alcohol lessens anxious apprehension and thus decreases the likelihood of a panic attack. In alcoholics, alcohol increases CO_2 sensitivity and promotes panic.

As far as PD(A) patients are concerned, the self-medication hypothesis appears to be valid. In the case of alcoholic patients, the hypothesis that alcohol may trigger the onset of panic is most likely.

CONCLUSIONS

Findings from the present review support the higher than expected rate of co-occurrence of PD(A) and alcohol use disorders, and document a familial aggregation and a familial transmission. The findings also suggest that, when panic onset is prior to alcohol use disorder, the use of alcohol is an attempt to self-medicate. At the same time, the findings suggest that when alcohol use disorders occur prior to PD(A), panic follows as a consequence of hypersensitization.

We started with 2 opposite hypotheses of causality that were apparently mutually exclusive. The first depicted alcohol use disorders as a complication of panic, thus supporting the self-medication theory. The other suggested that panic is a complication of alcohol use disorders.

We propose that these 2 hypotheses are opposite, but not mutually exclusive. The first may explain the mechanism of the comorbidity when panic occurs prior to alcohol use, the latter when alcohol use disorders are temporally prior to panic.

However, the issues proposed in the present review require further clarification. In fact, we found only 20 studies that met our strict inclusion criteria over a time span of about 20 years. What are needed are additional studies using well-standardized methods, followed by reliable replications.

Moreover, studies clarifying the temporal occurrence of the 2 disorders are warranted. They could have interesting clinical implications and solve the dilemma on how to treat dually diagnosed patients. If PD(A) occurs first, a specific psychopharmacologic antipanic treatment could be applied early. If alcohol abuse occurs first, the biochemical process of hypersensitization should be addressed early, preventing withdrawals and promoting sobriety. Alternatively, a parallel treatment approach or an integrated treatment program could be useful.

In this frame, treatment research should be encouraged to define the pharmacologic/nonpharmacologic program to apply when panic and alcoholism co-occur. It also would be interesting to establish if the treatment of panic has an impact on drinking habits, for instance reducing alcohol consumption or improving withdrawal symptoms, and if this activates a virtuous circle further improving panic symptoms.

Finally, to draw a more complete picture, it would be interesting to verify if the hypotheses proposed in the present review can be applied to the relationship between panic and other substances of abuse. In fact, it is widely accepted that panic may begin or be exacerbated by the use of drugs such as marijuana, cocaine, and amphetamines and that in sedative/hypnotic abusers there is an increasing rate of panic. In practice, it would be interesting to verify the temporal relationship between panic and abuse of other substances and, once again, identify the proper treatment for dually disordered patients. This would imply addressing the substance dependence as well as using pharmacologic/nonpharmacologic treatments for panic.

In general, increasing the knowledge on panic and substance abuse should guarantee that more instruments are used in clinical practice to treat patients, prevent complications, and improve their quality of life.

Drug names: clonazepam (Klonopin and others), imipramine (Tofranil and others).

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