Alcohol and Substance Abuse in Panic Disorder

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The relationship between panic disorder and alcohol and substance abuse is well known but not clearly understood. Various theories have been proposed to explain the increased comorbidity of these two disorders. Patients may be self-medicating for anxiety symptoms or be genetically predisposed to this dual diagnosis. Whatever the cause, patients with panic disorder who abuse alcohol or other substances require careful attention from the clinician. To effectively treat the patient, both conditions must be taken into account when formulating a treatment plan.

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The relationship between anxiety and alcohol and substance abuse has long been culturally acknowledged. With the continuing evolution of diagnostic methodologies, increasing attempts have been made to more accurately delineate the extent and cause of this relationship, particularly that of anxiety and alcohol abuse. The relationship between anxiety and abuse of other substances has been considerably less well studied.

Research efforts are difficult to summarize because of factors that hamper data interpretation. Among these are different populations (i.e., clinical versus epidemiologic studies), small numbers of subjects, use of differing criteria for alcohol and drug abuse, lack of delineation of specific anxiety disorders, and confusion of anxiety symptoms with anxiety disorders. Schuckit and Hesselbrock[1] have described several other factors, including not controlling for the presence of a third disorder (e.g., stimulant abuse) and perhaps most critically not controlling for withdrawal phenomena. For example, in some studies, as many as 80% of alcohol-dependent men admitted to repetitive panic attacks in the course of withdrawal from alcohol.[2]

PREVALENCE

Studies of the general population estimate a lifetime prevalence of alcohol abuse and dependence at 13.5% to 14.1%, with other drug abuse or dependence at 6.1%.[3,4] Anxiety disorders, skewed by a high rate of phobias, appear to have a lifetime prevalence of 10% to 25% in the general population. Panic disorder is diagnosed in approximately 1.4% to 3.5% of the general population.[3] Between 4% and 8% of persons in the general population have agoraphobia.[5]

Studies examining the relationship between alcohol abuse and anxiety and panic disorder have taken two approaches. In the first, anxiety disorders are studied in persons with variously defined alcohol- or substance-related problems. These studies have produced a broad range of estimates—from 22.6% to as high as 68.7%—of the proportion of substance-abusing persons who have anxiety problems.[6] In a recent review of 10 studies of panic disorder in alcohol-abusing patients, Schuckit and Hesselbrock[1] reported similar figures. However, they calculated a "gross adjusted rate" by attempting to exclude temporary organic conditions and include, where possible, the anxiety disorders that developed before the alcohol dependence and abuse. This adjusted figure ranged from 2% to 17%, with a summarized mean at 6%. (The authors believe this is still an exaggerated figure.) This estimate is somewhat higher than the lifetime rate for panic disorder in the general population.

Schuckit and Hesselbrock[1] applied similar methodology to seven studies of agoraphobia and alcohol abusers. The unadjusted prevalence rates of agoraphobia among alcoholics ranged from 2% to 41%. The overall "gross adjusted rate" had a mean of 9%, again somewhat higher than the prevalence of agoraphobia in the general population. Other investigators[7] have suggested that as many as 64% of cocaine users experience panic attacks.

In an alternative approach, Regier et al.[4] reported that 17.1% of persons with diagnosed anxiety disorders abuse alcohol, slightly higher than community rates for alcohol abuse alone. The highest rates of alcohol abuse appeared to be among agoraphobic patients who experience panic attacks.[8]

A number of studies have also examined the extent of alcohol abuse among patients with panic disorder.[1] These studies found a rate of alcoholism similar to that in the

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general population, with the exception of a study by Reich and Chaudry,[9] who found that 28% of 61 patients with panic disorder had a lifetime history of alcoholism. However, this drug treatment study solicited participants to study the effectiveness of alprazolam. Overall, the more tightly defined the anxiety disorder (i.e., panic disorder or agoraphobia, or both), the lower the prevalence rates.

ORDER OF DISORDER ONSET

Investigators have attempted to discover which disorder occurs first as a means of understanding how the disorders are related. Few articles specifically address the time of onset of panic disorder or agoraphobia as it relates to the substance abuse. In a 1990 literature review, Kushner et al.[6] reported that the evidence for panic disorder was mixed and that various studies described onset before, simultaneously with, and after alcohol problems. The authors noted that agoraphobia more consistently preceded the onset of alcoholism. Schuckit and Hesselbrock,[1] however, concluded that the "more vigorous" studies indicated that in at least two thirds of persons with both psychiatric and alcohol-related disorders, the alcohol syndrome occurred first. An example of a more rigorous finding is that from a 40-year follow-up of college students that revealed no evidence of antecedent anxiety disorder for alcoholism.[10] As Stockwell and Bolderston[11] point out, these conflicting data may result because patients are likely to report the first symptom of nervousness they experience, even though this may not be a full-blown diagnosable disorder.

WHY THE RELATIONSHIP?

Several theories have been proposed regarding the higher-than-expected comorbidity of panic disorder and alcohol or substance abuse. An historically prominent hypothesis is that of self-medication, more formally known as the tension-reduction theory of alcohol abuse.[12] This theory posits that reducing aversive affective or physiologic states maintains the relevant substance abuse behavior; in other words, patients are medicating themselves for anxiety symptoms. This theory takes a commonsense approach, and many patients endorse the concept. Alcohol as an anxiolytic is consistent with observed cross-tolerance with benzodiazepines, providing a possible mechanism of action for anxiety reduction. However, evidence for the efficiency of alcohol in reducing panic attacks is mixed.[11–14] Substantial evidence indicates that alcohol, when used on a prolonged basis or in fairly high doses, can heighten anxiety.[15] Withdrawal from alcohol clearly produces panic-like symptoms (if not the disorder itself), and a number of studies have shown that phobic fears are not always alleviated by ingesting alcohol.[16–18] Some fears are unaffected or even worsened.

Another explanation for the relationship between alcohol or substance abuse and panic disorder is a possible genetic link between the disorders. However, studies examining this hypothesis have yielded mixed results. Several investigators[19,20] have reported rates of alcoholism among male and female relatives of patients with panic disorder similar to or less than those for the general population. Two other studies[21,22] found only slightly higher than expected rates of alcoholism among relatives of persons with panic disorder. Yet Noyes et al.[23] reported significantly higher than expected rates of alcoholism among relatives of persons with agoraphobia. Harris and Noyes[24] also found a higher incidence of alcoholism among the male relatives of agoraphobic probands. Thus the literature does not consistently support a family crossover, although a genetic link may be a factor, particularly in agoraphobia. Further study is needed.

Another possibility is that anxiety symptoms are stimulated by unstable personal environments related to alcohol dependency. Alcohol-dependent persons are more likely to have grown up in chaotic environments resulting from parental pathology. Continued alcohol problems in adulthood may cause social and occupational stressors that further contribute to the activation of anxiety disorders.[1]

Various theories suggest that the effects of alcohol on cognitive states may at least partly explain the alcohol-panic association. The anxiolytic effects of alcohol are more pronounced when the condition has a substantial cognitive component, such as in anticipatory anxiety or agoraphobia.[25] Other evidence suggests that alcohol consumption may narrow individuals' perception of more immediate cues, thus protecting them from being overwhelmed by environmental stimuli.[26] Interference with natural desensitization by individuals' attribution (to the drug) of positive outcomes and a subsequently reduced view of their own self-efficacy also may play a role.[27]

ALCOHOL-PANIC BIOLOGICAL CONNECTION

Recently, there has been increased interest in and a spate of hypotheses regarding psychobiological disturbances and how they may account for symptom overlap and the comorbidity of alcoholism and panic disorder.[17,28,29] A complete discussion of this topic is not possible here (see George et al.[17] for an excellent review). Briefly, ingestion of or withdrawal from alcohol may increase levels of norepinephrine in the central nervous system, which may be related to evidence of increased noradrenergic activation (locus ceruleus) in patients with panic disorder. Persons who are chronic alcoholics also exhibit dysregulation of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA).[30]

Repeated alcohol withdrawal may cause a kindling process, a concept originally applied to patients with seizure disorders. This phenomenon consists of precipitating

seizures (i.e., lowering the seizure threshold) by repeated, intermittent subconvulsive stimuli. Both the GABA and catecholamine systems have been implicated in this process. Most evidence for the kindling phenomenon is based on the effects of heavy alcohol consumption and subsequent withdrawal. A number of studies have demonstrated hyperexcitability of the central nervous system, especially of limbic structures such as the hippocampus, associated with alcohol withdrawal syndrome.[31] Evidence of excitability in the same brain regions implicated in panic disorder suggests that alcohol withdrawal may have a kindling effect, resulting in panic symptoms or panic disorder. Post[32] suggested that periodic cocaine use also could lead to panic disorder.

Although other biological systems remain to be studied, the known neurophysiology of panic attacks and alcohol intoxication and withdrawal suggest that a similar mechanism may contribute to their comorbidity.

TREATMENT IMPLICATIONS

Treatment of patients with both alcohol abuse (or substance abuse) and panic disorder is often focused on one condition without recognition of or regard for the other. Despite differences in data interpretation, ample evidence suggests a high comorbidity that should increase clinicians' suspicions and awareness. A willingness to specifically question patients regarding signs and symptoms of these disorders, especially alcohol and substance abuse, is the first step. Studies[33] have shown that an accurate pretreatment evaluation is the best predictor of treatment response. A comprehensive approach also is indicated. Quitkin et al.[34] have shown that treating the anxiety disorder may improve outcomes in drug-abusing patients.

Where possible, the clinician should determine which disorder is primary (i.e., which began first). If the alcoholism seems primary, a full panic disorder treatment program probably should be delayed (for 2, 3, or up to 8 weeks) to lessen the likelihood that the panic symptoms or attacks are withdrawal phenomena. Of course, symptomatic anxiety control may be needed in the interim. The patient must be educated about the contributions of drugs or alcohol to their panic attacks. Some may be aware of this connection, but most are not.

The presence of an active or past history of alcohol abuse requires extra caution when selecting drug therapy. In the past, tricyclic antidepressants have been drugs of choice, but the increased risk of suicide with this class of drugs may change that view. These drugs also can lower seizure thresholds. Clinicians should be aware that, for similar doses, blood levels of tricyclic antidepressants may be lower in alcoholic patients than nonalcoholic patients, secondary to differential clearance of the drug,[35] and may affect clinical response. Desipramine has been reported to be useful for cocaine-related panic attacks.[36]

Monoamine oxidase inhibitors, which are clearly effective for panic disorder, may be problematic for drug- or alcohol-abusing patients. These patients may be less likely to comply with the food and beverage restrictions necessary to prevent a possible hypertensive crisis.

Serotonin selective reuptake inhibitors are effective in some patients with panic disorder and less lethal in overdose. Thus, serotonin selective reuptake inhibitors might be considered drugs of choice for first-line treatment of alcoholic patients with panic disorder. Small starting doses may be required if increased anxiety or agitation occurs, especially during the alcohol withdrawal period.

The use of benzodiazepines in dually diagnosed patients remains controversial, perhaps more so than warranted. A recent review of benzodiazepine liabilities among alcoholic persons found that well-designed studies did not clearly support the common Alcoholics Anonymous position[37] regarding these drugs. This group is opposed to benzodiazepines, citing "devastating dependence." (They also are opposed to all psychotropic medications.) Ciraulo et al.[38] concluded that alcoholics as a group may be more susceptible to benzodiazepine abuse than nonalcoholics, but there is little evidence to suggest that all or even most alcoholic patients abuse these drugs. The authors concluded that, when rationally prescribed, benzodiazepines are fairly safe drugs with multiple uses in treating alcohol-abusing patients.

The nonpharmacologic aspects of treating dually diagnosed patients also may require special accommodation. The continuing use of alcohol or other abused substances, particularly by patients with agoraphobic avoidance, may sabotage therapeutic efforts. Some evidence suggests that the use of alcohol interferes with the efficacy of exposure treatment.[14]

CONCLUSION

The increased comorbidity of panic disorder and alcoholism has been demonstrated in both clinical and epidemiologic studies, although there is no consensus on the exact prevalence of this comorbidity. Several theories have been offered regarding the relationship of panic disorder and alcohol or substance abuse; most likely, this relationship results from multiple interacting factors. Recognizing the coexistence of these disorders is paramount, since treatment decisions may be altered by this information.

Drug names: alprazolam (Xanax), desipramine (Norpramin and others).

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Discussion

Treating the Substance-Abusing Patient

Dr. Pollack: What is your approach to treating a patient with panic disorder who has a history of abusing alcohol?

Dr. Ballenger: This is a controversial area. The consensus seems to be that you should try everything, including tricyclic antidepressants and serotonin selective reuptake inhibitors (SSRIs), before using a benzodiazepine. On the other hand, there are several anecdotal reports of clinicians who do not like benzodiazepines but ultimately end up using them in patients with significant anxiety and alcohol problems. It is possible that alcoholic patients with panic disorder do not have as much trouble with benzodiazepines as persons with alcoholism alone.

Dr. Marshall: Some clinicians believe that alcohol-abusing patients are more likely to become addicted to benzodiazepines, although there is no good evidence to support this. Others believe that abstinent alcoholic patients given benzodiazepines will be more likely to go back to drinking.

Dr. Pollack: I have seen that happen, but it's rare. It tends to occur in patients taking high doses of alprazolam, which makes them become disinhibited.

Before prescribing a benzodiazepine to an alcoholic patient, I would consider the patient's personality—whether they are obsessive or totally passive. Impulsivity is a negative characteristic for considering benzodiazepines. However, patients who are willing to take some responsibility for treating their disorder may be candidates for benzodiazepine treatment.

Dr. Davidson: The order of onset also is a factor. Patients whose alcoholism began after the onset of panic disorder may be attempting to self-medicate. If we explain

that drinking is an effort to self-treat, they may be more willing to cooperate with some other form of treatment.

Dr. Jefferson: How would you treat a patient with panic disorder who currently is abusing alcohol?

Dr. Rosenbaum: We see a significant number of patients at our center who are alcohol dependent. When these patients come in, they clearly meet the criteria for panic disorder or another type of anxiety disorder. Yet when these patients are interviewed again 6 weeks after they become abstinent, they no longer have the panic symptoms. This is also true of depression.

Dr. Ballenger: I think this emphasizes the need to help these patients stop drinking. We probably should have them abstain from alcohol for at least 6 weeks before we attempt to treat the panic disorder. This applies to patients who had panic disorder before they began drinking, as well as to those who experienced panic symptoms after they began drinking.

Our approach is to use withdrawal and counseling to get patients to stop drinking. For acute withdrawal, we prescribe chlordiazepoxide, but otherwise patients are medication free during the withdrawal period, even if they experience panic attacks.

Dr. Jefferson: At many detoxification centers, patients can withdraw from alcohol with just good nursing care, without any medications.

Dr. Marshall: In general practice, most physicians encounter patients who have prominent anxiety and some degree of alcohol abuse, but who are not flagrantly dependent on alcohol.

Dr. Ballenger: I think it is often impossible to tell these patients to completely abstain from alcohol before initiating some sort of therapy. I usually start my patients on a medication other than a benzodiazepine, such as an SSRI. This gives me time to evaluate the patient, establish a relationship, and determine whether the patient complies with the treatment. If patients do not respond or only partially respond, I introduce a benzodiazepine.

Dr. Jefferson: The use of SSRIs in alcoholic patients is interesting. Some studies have found that the SSRI decreases the reward from alcohol.

Dr. Pollack: When a benzodiazepine is indicated in an alcohol-abusing patient, I recommend using a longer-acting formulation with a more gradual onset of effect to decrease the "buzz" patients get from it.

Dr. Charney: How effective are psychotherapies in an alcohol-abusing patient with panic disorder?

Dr. Barlow: In previous studies, we have always excluded active substance abusers. In a small study under way now, we are specifically treating alcohol-abusing patients and monitoring their abuse. However, results are not yet available.

Dr. Pollack: A recent study has shown that low-dose benzodiazepines facilitate behavior therapy.

Dr. Rosenbaum: That finding relates to our previous discussion—that many patients in trials of cognitive behavior therapy are using low-dose benzodiazepines when they are enrolled and throughout the study period.

Dr. Davidson: It may be that the combination of behavior therapy and low-dose benzodiazepines is so effective not because of the combination per se, but because the benzodiazepine is not discontinued.

Dr. Shear: Yet this relationship is not straightforward either. I've had several patients who actually felt better after discontinuing alprazolam; one of these patients wanted no further treatment at all.