Anxiety Sensitivity in Patients with Alcohol Dependence: A Cross-Sectional Case-Control Study

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Abstract

Anxiety Sensitivity (AS) is a cognitive risk and maintenance factor for anxiety disorders, and it consists of three dimensions: Physical concerns, Cognitive concerns, and Social concerns. No study has investigated the role of AS in individuals with Alcohol-Dependence (A-D), comparing a group of patients with Alcohol-Dependence (A-D) to patients with Anxiety Disorders (AD) and healthy individuals on AS dimensions. Specific dimensions of AS might play a role as cognitive vulnerability and maintenance factors also for A-D-related problems. Examination of AS in patients with A-D might inform clinical practice and public health policy suggesting the integration of treatments specifically targeting AS in A-D patients. The current study aimed to explore the relationship between AS dimensions and A-D. One hundred twenty-five participants, including patients with a diagnosis of A-D (n= 35), patients with a diagnosis of any Anxiety Disorder (AD) (n= 40) and healthy individuals as a control group (CG) (n= 50) completed the ASI-3, STAI-Y and BDI-II. After controlling for anxious traits, A-D patients had stronger Social concerns. Physical and Cognitive concerns appeared, however, significantly more severe among the AD group than the other two groups. Given the strong association between Social concerns and A-D, treatments for A-D patients should also target Social concerns. Study limitations, implications for mental health policy and intervention programs are addressed.

Keywords: Anxiety Sensitivity, Alcohol-Dependence, Anxiety Disorders, Cognitions, Cognitive Behavioural Therapy


1. Introduction

1.1. The Construct of Anxiety Sensitivity

Anxiety Sensitivity (AS) has been conceptualized as the fear of arousal-related sensations arising from beliefs that such sensations have harmful consequences, including an impending heart attack, social rejection or insanity [1]. AS has been believed to be an amplifier of negative states and, consequently, a risk factor for the development of anxiety-related psychopathology [1]. This hypothesis has been supported by several studies [2]. In a recent meta-analysis, Olatunji and Wolitzky-Taylor [3] reported that AS levels were greater among patients with anxiety disorders, compared to undergraduate controls. Prospective studies have found that AS can play a role as a risk factor for the development of clinically meaningful anxiety symptoms [4].

Originally proposed as an unidimensional construct, AS has been recently conceptualized as consisting of three dimensions: Physical concerns, Cognitive concerns, and Social concerns [5]. The Anxiety Sensitivity Index-3 (ASI-3) [6] is an instrument developed and validated to measure three dimensions of AS. In the validation study [6], patients with a diagnosis of panic disorder (PD), but not the control group and groups with other anxiety disorders, showed significantly higher scores on the Physical concerns subscale; conversely, patients with Social Anxiety (SA) showed higher scores in on Social concerns. Wheaton, Deacon, McGrath, Berman, & Abramowitz [7] observed that patients with PD, SA, and Obsessive-Compulsive Disorder (OCD) had significantly higher total scores than the control group, but the authors did not find differences between the clinical groups on the Physical concerns subscale scores [7]. Patients with SA, but not controls and other clinical groups, reported higher scores on the Social concerns subscale. Patients with any anxiety disorder or OCD had significantly higher scores than controls on the Cognitive concerns subscale [7].

1.2. Anxiety Sensitivity and Alcohol Consumption
The hypothesized relationship between AS and avoidance behaviors [8] has led researchers to investigate the role that this cognitive vulnerability factor could have on the use of substances, including alcohol [9]. The use of alcohol could have the function of reducing arousal [9]. DeMartini and Carey [10] have developed a model on the relations between AS, alcohol consumption, and drinking motives. According to the authors, AS might affect anxiety symptoms, alcohol use and drinking motives (particularly coping/conformity motives) [10].

In the last two decades, a great deal of research has examined the relationship between AS and excessive alcohol use, and correlational researches have suggested that high AS is associated to increased alcohol consumption [10]. Stewart and colleagues [9] showed a significant correlation between AS and excessive alcohol consumption in a non-clinical sample of young women. Similar results were obtained from Conrad, Pihl, and Vassileva [11] on a non-clinical sample of young men. A significant association between AS and problematic alcohol use has been supported in a study on 245 students irrespective of gender [12], that indicated that AS was related to negatively reinforced drinking, positively reinforced drinking and temptation-motived drinking. Interestingly, in this study the association was found -most prevalent in males – between AS and heavily drinking in situations where the removal of unpleasant emotions was a primary motive to drinking. In contrast to literature findings, Novak, Burgess, Clark, Zvolensky, and Brown [13] have not found a direct association between AS and alcohol consumption levels, but they have noted that the sample recruited was relatively young, with an average age of 18.9 years for males and 19.4 years for females. The authors suggested that future studies should investigate whether anxiety sensitivity could predict not only current heavy drinking, but also heavy drinking sustained over a long period of time [13]. In a study conducted on young alcohol consumers, Howell, Leyro, Hogan, Buckner, and Zvolensky [14] have found that the distress tolerance was significantly related to coping motives for alcohol use, while AS was significantly related to conformity motives for drinking. The authors have hypothesized that individuals with high AS levels experienced elevated fears about the perceived negative effects of publicly observable anxiety symptoms (e.g., sweating), and therefore may be more motivated to use alcohol in public and to conform with alcohol-using actions of their peers [14].

Few studies have investigated the role of AS in samples of patients with alcohol abuse or alcohol-dependence. In two studies on patients with substance abuse including alcohol [15,16], high AS was a significant predictor of increased alcohol consumption in situations eliciting negative emotions, and the relationship remained significant after controlling for trait anxiety. The authors suggested that AS might be a predictor of abuse of certain substances [15]. In a two-year follow-up prospective study on students [17], high AS levels appeared to be a risk factor for alcohol use disorders (AUDs). The follow-up evaluations showed that high AS and being male exerted unique influences on the development of AUDs, irrespective of both trait anxiety and a history of substance use disorder [17].

1.3. Rationale for the Current Study

To our knowledge, no study has investigated the role of AS dimensions in individuals with Alcohol-Dependence (A-D), comparing a group of patients with A-D to a group of patients with Anxiety Disorders (AD) and a non-clinical control group (CG) on AS dimensions. Specific dimensions of AS might play a role as cognitive vulnerability and maintenance factors for A-D-related problems. Examination of AS in patients with A-D might inform practice and suggest the integration of therapeutic components specifically aimed at AS in the treatment of patients.

Indeed, given its importance in alcohol-related problems, treatment and prevention strategies for reduction of high AS have been evaluated with the aim to consequently target alcohol consumption [18]. Consistent with these suggestions, Watt and colleagues [18] for example, have noted a marginally significant reduction in the proportion of high-consequences drinkers in the high AS group, but no reductions in consumption.

1.4. Aims

The present study aimed to explore the relationship between AS dimensions and A-D. Specifically, levels of AS dimensions were compared between a group of patients with a primary diagnosis of A-D, a group of patients with a primary diagnosis of any anxiety disorder, but without problem alcohol-related or A-D, and a group of control participants.

2. Methods

2.1 Participants

Overall, 125 participants were recruited: 35 patients with a primary diagnosis of Alcohol-Dependence (A-D), 40 patients with a primary diagnosis of any Anxiety Disorder (AD) and 50 non-clinical participants recruited from the general population, who were used as a control group (CG). All the participants were adults (age≥18 years old), and they had Italian nationality. Patients were included in one of the two clinical groups if they fulfilled criteria for a primary diagnosis of A-D or AD. The AD group included patients with a primary diagnosis of panic disorder with or without agoraphobia (n= 11), generalized anxiety disorder (n= 27) and social phobia (n= 2). The primary diagnosis was conceptualized according to the following criteria: (a) the main psychiatric problem in terms of severity and functional impairment, (b) the problem was perceived by the patient as the primary source of distress, (c) the disorder was the problem for which the patient had required a treatment. The following criteria for the exclusion from each of the clinical groups were: (a) diagnosis of mental retardation or neurological syndromes, (b) diagnosis of psychosis or bipolar disorders, (c) participation in previous sessions of Cognitive Behavioral Therapy (CBT) in the past six months. In addition, participants in the AD group were excluded if they had a current or lifetime diagnosis of A-D, abuse of alcohol, drug abuse or dependence.

Patients with A-D were recruited from the Alcohol and Drug Service of Florence. In this group patients had a
mean age of 47.43 years old (SD= 8.23, range= 31-67), were predominantly males (62.90% of the group), and mainly reported having a job (68.60%). Patients with AD were recruited at the Mental Health Service of Florence, a community mental health outpatient service; these had an average age of 49.03 years (SD= 17.13, range= 18-83), were predominantly female (62.50%) and mainly reported having a job (35%) or to be retired (35%). CG group was recruited in a variety of public settings (universities, public employment settings, libraries); these had an average age of 48.38 years (SD= 16.27, range= 21-86 years), were predominantly female (74%) and mainly reported having a job (56%) or to be retired (24%).

An overview of socio-demographic descriptive characteristics of three groups is shown in Table 1.

| Table 1. Descriptive socio-demographic characteristics of A-D, AD and CG groups |
|---------------------------------|-----------------|-----------------|-----------------|
| Age (years)                     | M (SD; range)   | M (SD; range)   | M (SD; range)   |
| A-D Group (n= 35)               | 47.43           | 49.93           | 48.38           |
| AD Group (n= 40)                | (8.23; 31-67)   | (17.13; 18-83)  | (16.27; 21-86)  |
| CG Group (n= 50)                |                 |                 |                 |

<table>
<thead>
<tr>
<th>Sex</th>
<th>n (%)</th>
<th>n (%)</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>22 (62.90)</td>
<td>15 (37.50)</td>
<td>13 (26.00)</td>
</tr>
<tr>
<td>Marital Status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single/Unmarried</td>
<td>13 (37.10)</td>
<td>14 (35.00)</td>
<td>19 (38.00)</td>
</tr>
<tr>
<td>Married/Cohabiting</td>
<td>10 (28.60)</td>
<td>15 (37.50)</td>
<td>28 (56.00)</td>
</tr>
<tr>
<td>Separated/Divorced</td>
<td>12 (34.30)</td>
<td>9 (22.50)</td>
<td>2 (4.00)</td>
</tr>
<tr>
<td>Widower</td>
<td>0 (0.00)</td>
<td>2 (5.00)</td>
<td>1 (2.00)</td>
</tr>
<tr>
<td>Residence Area</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northern Italy</td>
<td>2 (5.70)</td>
<td>2 (5.00)</td>
<td>4 (8.00)</td>
</tr>
<tr>
<td>Central Italy</td>
<td>32 (91.40)</td>
<td>38 (95.00)</td>
<td>43 (86.00)</td>
</tr>
<tr>
<td>Southern Italy</td>
<td>1 (2.90)</td>
<td>0 (0.00)</td>
<td>3 (6.00)</td>
</tr>
<tr>
<td>Graduation degree</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elementary school</td>
<td>1 (2.90)</td>
<td>3 (7.50)</td>
<td>4 (8.00)</td>
</tr>
<tr>
<td>Mid school</td>
<td>16 (45.70)</td>
<td>10 (25.00)</td>
<td>5 (10.00)</td>
</tr>
<tr>
<td>High school</td>
<td>9 (25.70)</td>
<td>23 (57.50)</td>
<td>24 (48.00)</td>
</tr>
<tr>
<td>Degree and/or PhD</td>
<td>9 (25.70)</td>
<td>4 (13.00)</td>
<td>17 (34.00)</td>
</tr>
<tr>
<td>Employment status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>University student</td>
<td>0 (0.00)</td>
<td>4 (10.00)</td>
<td>4 (8.00)</td>
</tr>
<tr>
<td>Unemployed</td>
<td>8 (22.90)</td>
<td>8 (20.00)</td>
<td>7 (14.00)</td>
</tr>
<tr>
<td>Employed</td>
<td>24 (68.60)</td>
<td>14 (35.00)</td>
<td>28 (56.00)</td>
</tr>
<tr>
<td>Retired</td>
<td>3 (8.60)</td>
<td>14 (35.00)</td>
<td>11 (24.00)</td>
</tr>
</tbody>
</table>

Note: A-D= Alcool Dependence patients; AD= Anxiety Disorders patients; CG= Control Group.

2.2. Measures

All the participants completed a packet of self-report questionnaires including the ASI-3 [6], the State-Trait Anxiety Inventory-Y form trait subscale (STAI-Y) [19] and the Beck Depression Inventory-II (BDI-II) [20].

The ASI-3 is an 18-item self-report questionnaire on a 5-point Likert-type scale ("very little"= 0, "very much"= 4). ASI-3 is used to measure the three dimensions of AS: Physical concerns (eg. "When I feel pain in my chest, I worry that I'm going to have a heart attack"), Cognitive concerns (eg. "When I cannot keep my mind on a task, I worry that I might be going crazy") and Social concerns (eg. "I worry that other people will notice my anxiety"). High scores on each subscale reflect levels on that specific AS dimension. The original version of the ASI-3 [6] has shown to have good to excellent internal consistency indices in both clinical and non-clinical samples from different countries (range of Cronbach's alpha coefficients= 0.73-0.91). The Italian version has been shown to have good to excellent internal consistency indices in both non-clinical and clinical samples (range of Cronbach's alpha coefficients= 0.77-0.90) and a 2-month-test-retest reliability from good to moderate (Pearson's r = 0.62-0.71). In the current study internal consistency of the ASI-3 subscales was very good or excellent for the A-D group (range of Cronbach's alpha coefficients= 0.82-0.93), very good for the AD group (range of Cronbach's alpha coefficients= 0.82-0.89), and good for CG group (range of Cronbach's alpha coefficients= 0.81-0.92).

The STAI-Y [19] is a 40-item self-report questionnaire on a 4-point Likert-type scale ("not at all"= 1, "very much"= 4). In this study we used the Y-form of the questionnaire, consisting of 20 items measuring state anxiety (e.g., "I am tense") and 20 items measuring trait anxiety (e.g., "I worry too much over something that really doesn’t matter"). High scores on both the scales indicate high scores of trait or state anxiety, respectively.

In the present study the internal consistency of the subscales was very good for the A-D group (range of Cronbach's alpha coefficients= 0.86-0.88), very good or excellent for the AD group (range of Cronbach's alpha coefficients= 0.85-0.91) and good for the CG group (range of Cronbach's alpha coefficients= 0.78-0.79).

The BDI-II [20] is a 21-item self-report questionnaire on a scale ranging from 0 to 3, used to measure severity of depression symptoms in adult and adolescent patients with 13 years of age or older. In this study internal consistency was very good for the A-D group (Cronbach's alpha= 0.87), excellent for the AD group (Cronbach's alpha= 0.92) and very good for the CG group (Cronbach's alpha= 0.89).

2.3. Procedure

Data were collected from January 2013 to April 2014. Participants completed the measures individually or in small groups. Diagnoses assigned to the two clinical groups were made using a semi-structured clinical interview independently conducted by a psychiatrist and a psychologist, according to the DSM-IV-TR diagnostic criteria [21]. Participants in the CG group were unscreened with the aim to obtain a sample representative of the general population. In line with the Ethical Principles of Psychologists and code of conduct [22], all the participants gave written informed consent to participate in the study after having received an oral and written description about its purposes. For the recruitment of the two clinical groups, ethical approval has been obtained from the committees of the mental health services.

2.4. Statistical Analysis

In order to investigate differences between A-D group, AD group and CG group on ASI-3 total scores and subscales, STAI-Y-trait anxiety and BDI-II, were conducted one-way variance analysis with random effects models and multiple comparisons post-hoc with Fisher's Least significance Difference (LSD) test of significance. Power calculations were performed for this analysis. For a medium ES, 80% power, and a significance set at the level described above, the required sample size was. Between-group effect sizes (ES) were estimated using the partial eta squared index as recommended by Olejnik and Algina [23]. ES of 0.01, 0.06, 0.14 were interpreted as small, medium, and large, respectively [23]. Level of
significance chosen for the analysis has been subjected to a Bonferroni correction (p < .003).

3. Results

3.1. Differences on AS Dimensions between A-D, AD and CG Groups

Results of the one-way ANOVA showed a statistically significant difference between the three groups on the ASI-3 total scores [F(123, 2) = 22.85, p < .003] with a large effect size (partial η² = 0.30). A statistically significant difference among the three groups emerged also on the Physical concerns subscale scores [F(123, 2) = 21.58, p < .003] with a large effect size (partial η² = 0.29), on the Cognitive concerns subscale scores [F(123, 2) = 25.90, p < .003], with a large effect size (partial η² = 0.32), and on the Social concerns subscale scores [F(123, 2) = 8.26, p < .003] with a large effect size (partial η² = 0.13).

In a post-hoc test conducted with the Least Significant Difference (LSD), the AD group reported significantly higher scores on the Physical concerns subscale (M = 14.07, SD = 7.21) compared to the A-D group (M = 7.97, SD = 6.30) and the CG group (M = 5.14, SD = 3.15). The AD group reported significantly higher scores on the Cognitive concerns subscale (M = 11.40 SD = 6.33) than the A-D group (M = 6.34, SD = 5.60) and the CG group (M = 2.97, SD = 2.55). In contrast, the A-D group reported higher scores on the Social concerns subscale (M = 11.47, SD = 6.30) compared to the AD group (M = 8.71, SD = 5.68) and the CG group (M = 6.58, SD = 3.13).

The average scores (standard deviations) of the A-D, AD and CG groups and differences between the three groups on the ASI-3 total and subscale scores are presented in Table 2.

Table 2. Average scores (standard deviations) of A-D, AD and CG groups on STAI-Y-trait anxiety, BDI-II and ASI-3, and significant tests on the comparison between the three groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>STAI-Y-trait</th>
<th>BDI-II</th>
<th>ASI-3 Total</th>
<th>ASI-3 Physical</th>
<th>ASI-3 Social</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-D (n=35)</td>
<td>M(SD) = 58.67(9.37)</td>
<td>M(SD) = 14.97(10.21)</td>
<td>M(SD) = 21.48(15.06)</td>
<td>M(SD) = 7.97(6.30)</td>
<td>M(SD) = 11.47(6.30)</td>
</tr>
<tr>
<td>AD (n=40)</td>
<td>M(SD) = 48.23(12.22)</td>
<td>M(SD) = 25.14(13.45)</td>
<td>M(SD) = 35.05(15.16)</td>
<td>M(SD) = 14.07(6.72)</td>
<td>M(SD) = 8.71(5.68)</td>
</tr>
<tr>
<td>CG (n=50)</td>
<td>M(SD) = 42.88(11.49)</td>
<td>M(SD) = 10.11(8.79)</td>
<td>M(SD) = 14.94(6.75)</td>
<td>M(SD) = 5.14(3.15)</td>
<td>M(SD) = 6.58(3.13)</td>
</tr>
</tbody>
</table>

Note: A-D= Alcohol-Dependence; ASI-3= Anxiety Sensitivity Index-3; BDI-II= Beck Depression Inventory-second edition; AD= Anxiety Disorders; CG= Control Group; STAI-Y-trait= State and Trait Anxiety Inventory- trait anxiety.

4. Discussion

4.1. Summary of Findings

To our knowledge, the current study is the first contribution investigating differences in AS dimensions among patients with A-D, patients with AD and control individuals.

Consistent with previous data on the association between AS and alcohol consumption [3, 11, 12, 13, 15, 16, 24, 25, 26], findings showed that the AD group endorsed more severe Physical and Cognitive concerns than the other two groups.

Higher levels of Physical concerns, however, were found in the A-D group compared with the CG group. Thus, it could be hypothesized that Physical concerns serve as a transdiagnostic cognitive factor common to different types of mental disorders, and it could be related also to other forms of psychopathology, including A-D.

Cognitive concerns were more prevalent among patients with AD, compared to patients with A-D and controls. Higher levels of Cognitive concerns were also found in the A-D group compared to the CG group. It could be speculated that Cognitive concerns represent a relatively non-specific construct of generalized anxiety and worry [27], which has been found to be common in patients with A-D problems who are engaging in abstinence from alcohol use [27]. Moreover, such findings could also be related to the fact that the AD group, which mainly consisted of outpatients on treatment based on withdrawal from alcohol use, had strong fear of relapse from alcohol abstinence and its consequences leading to Cognitive concerns. This explanation seems to be supported by some elements of the Clark’s cognitive theory of panic [28]. Clark suggested that when an individual interprets a benign arousal-related sensation catastrophically (e.g.: Cognitive concerns), his/her perception of threat is enhanced, leading to increased severity of arousal symptoms (through a vicious circle leading to increase Physical concerns), and some types of safety behaviours like avoidance, for example, related to fear of negative judgments of others because of physiological responses such as sweating (e.g.: Social concerns). This logical path is supported by a range of studies on the association between Cognitive concerns and symptoms of social anxiety. A recent study has shown that Cognitive concerns were a significant unique predictor of...
social anxiety symptoms [29]. Individuals with higher levels of Cognitive concerns may fear that loss of control of their mental faculties could result in the publicly implementation of strange behaviours that can lead to embarrassment [26]. In addition, some research has demonstrated that Cognitive concerns were strongly associated with avoidance behaviors typical of social anxiety rather than social fear [30], and this could explain the connection between social and cognitive dimensions of AS.

Another interesting result was that patients with A-D reported stronger Social concerns relative to controls and patients with AD, and this result contrasted with a large body of literature indicating that Social concerns are mainly associated to AD, particularly social anxiety disorder, to the anxiety sphere in general [25], fear of negative evaluation and inhibited behavior in public [29], fear and avoidance of public situations and performances [26], anxiety in social interactions and diagnosis of social phobia [7]. It could be hypothesized that alcohol consumption may be a strategy to reduce physiological responses and to avoid fear of negative judgments, as reported by DeHaas and colleagues [15], who found that AS positively correlated with alcohol consumption as a coping strategy aimed to reduce negative emotions in unpleasant situations. As proposed by Howell and colleagues [14], drinkers with high AS could be motivated to use alcohol in social situations to conform with peers’ habits, since they could experience elevated fear of publicly observable anxiety symptoms.

4.2. Implications for Treatment Strategies and Policy

Results of this study have suggested a potential role of Social concerns in the development and/or maintenance of A-D. These may be useful in developing treatment strategies aimed at reducing this dimension of AS, such as treatment packages that literature on CBT has proven to be effective on social anxiety [31,32,33]. Most intervention programs use anxiety psycho-education (eg, identification of anxiety components and signals), cognitive restructuring (addressing overestimation or catastrophic thoughts) and enteroreceptive exposure (exposure to arousal-related sensations in order to learn to cope with them) [34]. Recent studies have suggested that these therapeutic strategies can be effectively applied also as a prevention or intervention strategy for individuals with problems related to dependence like tobacco dependence/abuse or alcohol misuse [18].

Given interventions that have had promising results on reduction of alcohol consumption with the aim of reducing high AS, a possible therapeutic proposal may refer to CBT techniques targeting Social concerns. Based on results from our study, interventions for social skills training in the treatment of these patients might be integrated in treatment of people suffering from alcohol problems. Consistent with this hypothesis, cognitive interventions specifically aimed to restructuring of the beliefs associated with the others’ judgment may be useful as a strategy to improve the effectiveness of programs to promote abstinence from alcohol and to prevent relapse. Through the psycho-education, social workers might explain anxiety, lapse and relapse mechanisms. In line with a modular therapeutic approach, a training to increase assertive skills, traditionally implemented in treatment of social anxiety patients, could be an additional component of the intervention on A-D.

4.3. Limitations and Implications for Research

Finally, some limitations of the current study should be pointed out. First, sample sizes of the three groups might have limited statistical power of the significance tests, thus leading to increased type II error probability. Further contributions on larger samples are required.

A second point concerns having recruited patients of the two clinical groups exclusively in two mental health centers; this limitation might affect external validity of the conclusions.

Another important limitation regards the impossibility to draw conclusions about the causal nature of the relationship between Social concerns and A-D.

In addition, the present study does not allow to clarify the role of Social concerns in the processes of relapse related to alcohol consumption. Therefore, future longitudinal studies are needed to investigate AS in relapse phenomena, thus providing additional guidance for the use of cognitive-behavioral techniques aimed to reducing AS and decreasing relapse risk in A-D patients.

In conclusion, current data showed that patients with A-D may have significant AS levels; in particular Social concerns could represent a target for treating relapse in people suffering from alcohol problems.

Conflicts of Interest

The authors have no conflict of interest to declare.

References