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# ANXIETY AS A PREDICTOR OF RELAPSE IN DETOXIFIED ALCOHOL-DEPENDENT PATIENTS

ULRIKE WILLINGER*, ELISABETH LENZINGER, KURT HORNIK[1], GABRIELE FISCHER, GEORG SCHÖNBECK, HARALD N. ASCHAUER and KURT MESZAROS on behalf of THE EUROPEAN FLUVOXAMINE IN ALCOHOLISM STUDY GROUP

Department of General Psychiatry, University Hospital for Psychiatry, Vienna and [1]University of Economics, Vienna, Austria

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**Abstract** — **Aims:** To evaluate the impact of mood, affect, and personality on predicting relapse in detoxified alcohol-dependent patients to uncontrolled drinking during a 1-year treatment study. **Methods:** A total of 521 patients with a DSM-III-R diagnosis of alcohol dependence, excluding those with major depressive disorder, took part in a European multicentre study (11 centres in the United Kingdom, Irish Republic, Switzerland, and Austria). Depressive symptoms were assessed using the Hamilton Depression Scale, whereas symptoms of anxiety were measured using the 'STAI-X2' of the self-rating scale State–Trait Anxiety Inventory and personality traits were measured by the Tridimensional Personality Questionnaire. **Results:** High anxiety as a stable trait, and personality traits such as high novelty seeking and low harm avoidance covering exploratory excitability, impulsiveness, extravagance, disorderliness and uninhibited optimism, predicted relapse. **Conclusions:** These measures could have a direct clinical application for predicting relapse to uncontrolled drinking in male and female detoxified alcohol-dependent patients. The findings indicate the importance of additional therapeutic treatment.

## INTRODUCTION

Symptoms of anxiety or depression, or personality traits, such as antisocial behaviour, conduct problems, violence, criminal acts, or personality disorders are frequently associated with alcohol dependence and sometimes precede it (American Psychiatric Association, 1994).

Reviewing laboratory, clinical, family, and prospective studies, Kushner *et al*. (2000) concluded that anxiety disorder and alcohol disorder could each initiate the other, and that the former can contribute to the maintenance of, and relapse into, pathological alcohol use. Driessen *et al*. (2001) concluded that severe trait anxiety persisting after 3 weeks of abstinence, co-morbid depressive and/or anxiety disorders, and combinations of these with moderate or severe current anxiety and depressive states are associated with increased risk of relapse in alcoholics.

Findings on the effect of depressive mood on the likelihood of returning to drinking are contradictory (Swendsen and Merikangas, 2000). For example, according to Heinz *et al*. (1999) and Driessen *et al*. (2001), depressed mood increases the relapse risk of abstinent alcoholics. Depressive symptoms were the most frequently endorsed relapse determinants reported retrospectively by men treated for alcohol addiction (Strowing, 2000). On the other hand, Greenfield *et al*. (1998) reported that depressive mood, measured by the Beck Depression Inventory (Beck and Steer, 1987), did not prospectively predict relapse in women or men.

Janowsky *et al*. (1999) suggested that specific personality variables have a predictive value. Personality traits, such as low conscientiousness and high neuroticism, are significantly related to a return to uncontrolled drinking following treatment (Fisher *et al*., 1998). Novelty seeking (NS), reflecting impulsiveness, measured by the Tridimensional Personality Questionnaire (TPQ), seems to identify a subgroup of alcohol-dependent men who are at risk for dropping out of treatment (Kravitz *et al*., 1999), and Basiaux *et al*. (2001) found higher scores in NS in alcohol-dependent patients in general.

In the present study of detoxified alcohol-dependent patients, we evaluated the impact of mood, affect and personality on predicting relapse to uncontrolled drinking during a 1-year treatment period, using multivariate analysis. In a previous analysis of the present database, Meszaros *et al*. (1999) reported that two personality dimensions of the TPQ predicted relapse in detoxified alcohol-dependent patients: NS emerged as a significant predictor for relapse in males over 1 year and there was a trend for harm avoidance (HA) to predict 'early' relapse (at 4 weeks) in females. However, in that analysis, adjustment was not made for the influence of mood and affect.

## SUBJECTS AND METHODS

### *Subjects and procedures*

A total of 521 patients with a diagnosis of alcohol dependence according to DSM-III-R (American Psychiatric Association, 1987) were included in a European multicentre study (11 centres in the United Kingdom, Irish Republic, Switzerland, and Austria). All patients gave written informed consent before entering the study. The sample consisted of 133 (26%) females and 388 (74%) males. The age at entering the study ranged between 19 and 72 years; the mean age (± SD) was 41.7 ± 9.7 years. The distribution of the marital status showed 243 (47%) married patients, 143 (27%) separated or divorced, 123 (24%) single, and 12 (2%) widowed. The mean age of onset ('age when drinking became a problem') was 21.5 ± 7.9. The median consumption in alcohol units [one unit was defined as 8 g of ethanol: i.e. a half pint of beer (4%), one glass of wine (11%), or one single measure of spirits (40%)] in a typical week during the most recent period of uncontrolled drinking was 140. The distribution of severity of alcoholism at baseline, measured by the Clinical Global Impression Severity subscore (National Institute of Mental Health, 1976) showed that

*Author to whom correspondence should be addressed at: University-ENT-Clinic, Waehringer Guertel 18–20, A-1090 Vienna, Austria.

the majority of our patients presented a 'moderately ill status' (33%), a 'markedly ill status' (25%) and a 'mildly ill status' (18%).

Subjects had to be detoxified and abstinent for 10–30 days before the baseline assessment. Exclusion criteria were pregnancy, breastfeeding, no adequate contraception, major depression, suicidality, seizure disorder, clinical medical illness, multiple drug allergies, and dependence on substances other than alcohol.

The study was a placebo-controlled, double-blind, prospectively randomized trial with the main objective of investigating the efficacy of fluvoxamine in reducing the number of detoxified alcohol-dependent patients relapsing to uncontrolled drinking (defined as consumption of ≥5 units of alcohol on one occasion and ≥4 such occasions in 1 week, or ≥12 units on one or more occasions) over a 1-year period. In addition, the ability of fluvoxamine to alleviate anxious and depressive symptoms and its safety in the long-term treatment of alcohol dependence were investigated.

The randomization was done after successful detoxification. The treatment (fluvoxamine/placebo) started at the time of the baseline assessment and finished after 1 year. Patients were assessed according to a standardized protocol procedure at 2, 4, 6, 8, 12, 16, 24, 32, 40 and 52 weeks after baseline. At these visits, safety and efficacy measures, including, in particular, information on relapse to uncontrolled drinking, were evaluated, and blood samples were drawn.

### *Measures*

In addition to other rating scales (reported in detail in Meszaros *et al*., 1996) the following were measured at baseline: the physician-rated 21-item version of the original Hamilton Depression Scale (HAMD) (Hamilton, 1960), the 'STAI-X2' of the self-ratable State–Trait Anxiety Inventory (STAI) (Laux *et al*., 1981), which enables anxiety to be quantified as a comparatively stable personality trait. Personality traits according to the Unified Biosocial Personality Model (Cloninger, 1987) were measured using the 100 items of the self-administered TPQ and are operationally defined by the three independent temperamental dimensions NS, HA and reward dependence (RD).

### *Statistical analyses*

Logistic regression analysis (Cooley and Lohnes, 1971) was conducted with relapse as the dependent variable and depression status, trait anxiety, and the three TPQ dimensions as independent variables. The treatment group (fluvoxamine or placebo) indicator was also used as an independent variable in order to adjust the results for a possible treatment effect. The treatment effect itself will be reported separately (J. Chick *et al*., unpublished data). All computations were performed using R (Ihaka and Gentleman, 1996). Patients who never reported relapse and missed no visit were considered as 'non-relapsers'. Relapsers are those patients who missed at least one visit, as well as drop-outs.

## RESULTS

Seventy-one patients (14.5%) (21 females and 50 males) showed no relapse to uncontrolled drinking during the 52-week observational period. There were no significant differences between females and males with respect to rate of relapse (females 16%, males 13%: $\chi^2 = 1.596$; df = 1; $P = 0.206$).

The logistic regression model (Table 1) showed that HA ($Z = –2.5$; $P = 0.01378$) and trait anxiety ($Z = 3.1$; $P = 0.00211$) were significant predictors for relapse in females, with lower HA and higher trait anxiety indicating a higher probability of relapse. RD ($Z = –0.2$; $P = 0.86605$), NS ($Z = –1.9$; $P = 0.05713$) and HAMD ($Z = 0.5$; $P = 0.64502$) had no significant influence on relapse in females. In males, NS ($Z = 2.5$; $P = 0.0134$) and trait anxiety ($Z = 5.6$; $P < 0.0001$) significantly influenced relapse with higher NS and higher trait anxiety indicating a higher probability for relapse. HA ($Z = –1.5$; $P = 0.1423$), RD ($Z = –1.3$; $P = 0.1894$), and HAMD ($Z = 1.3$; $P = 0.1989$) had no significant influence in males (see Table 1).

## DISCUSSION

The high relapse rate ( 85.5%) was similar to that in a recent 6-month UK study (Chick *et al*., 2000), but higher than that in many other studies. This might, in part, be due to a relatively low criterion included in our definition (40 g ethanol on four or more occasions per week). We did not find a significant influence of depressive symptoms on relapse to uncontrolled drinking. It is possible that this was an artefact of excluding from the study patients with major depressive disorder. We could not find a significant interaction between depressive symptoms and the kind of treatment for predicting relapse; therefore, we do suspect that the treatment with fluvoxamine in half the patients obscured the effect. Our result is similar to that of Greenfield *et al*. (1998).

RD, covering sentimentality versus tough-mindedness, perfectionist perseverance versus pragmatic quitting, attachment versus detachment, and dependence versus independence, was not associated with relapse. However, low HA in females, covering being carefree, relaxed, daring, composed, courageous, and optimistic even in situations that worry most people, was associated with relapse, as was high NS in males, covering

Table 1. Statistical indicators for the Tridimensional Personality Questionnaire (TPQ) scales, trait anxiety, and the Hamilton Depression Scale (HAMD) by gender

| Variables | Gender | Mean ± SD | *Z* | *P* |
|---|---|---|---|---|
| NS | Females | 17.0 ± 5.7 | –1.9 | 0.05713 |
| | Males | 18.5 ± 5.4 | 0.5 | 0.64502 |
| | Combined | 18.2 ± 5.5 | | |
| HA | Females | 21.2 ± 6.8 | –2.5 | 0.01378 |
| | Males | 18.4 ± 7.3 | –1.5 | 0.1423 |
| | Combined | 19.1 ± 7.3 | | |
| RD | Females | 20.3 ± 4.6 | –0.2 | 0.86605 |
| | Males | 18.7 ± 4.7 | –1.3 | 0.1894 |
| | Combined | 19.0 ± 4.7 | | |
| Trait anxiety | Females | 52.9 ± 5.4 | 3.1 | 0.00211 |
| | Males | 49.9 ± 5.8 | 5.6 | <0.0001 |
| | Combined | 47.6 ± 5.6 | | |
| HAMD | Females | 12.1 ± 9.3 | 0.5 | 0.64502 |
| | Males | 10.6 ± 7.8 | 1.3 | 0.1989 |
| | Combined | 11.9 ± 8.5 | | |

NS, novelty seeking; HA, harm avoidance; RD, reward dependence (all features of the TPQ).

being quick-tempered, exploratory, excitable, curious, enthusiastic, exuberant, easily bored, impulsive, and disorderly. The NS subscale score of the TPQ was also found to identify a subgroup of alcohol-dependent men who are at risk for dropping out of treatment (Kravitz *et al*., 1999). In the present study, we have shown that personality traits covering exploratory excitability, impulsiveness, extravagance, disorderliness, and uninhibited optimism were significantly related to the probability of returning to uncontrolled drinking in males and females.

We found that anxiety as a comparatively stable trait, more precisely high trait anxiety, is of a significant predictive value for relapse to uncontrolled drinking in both males and females. The predictive power of anxiety might be influenced by differences in addiction severity but there were no significant correlations between trait anxiety and the clinical global impression of the patients ($r = -0.05$; not significant), both measured at baseline, 10–30 days after detoxification. Anxiety symptoms often disappear rapidly after detoxification and treatment for these symptoms might not be necessary (Allan *et al*., 2002). Persisting severe anxiety symptoms may, however, lead to an increased risk of relapse (Driessen *et al*., 2001), which was also our finding.

Several studies reported the relationship between anxiety and alcoholism with causes of this association remaining controversial (e.g. Kushner *et al*., 2000). Three explanations are: (1) anxiety promotes alcoholism (self-medication); (2) alcoholism promotes anxiety; (3) both conditions promoted by a third factor.

The 'self-medication hypothesis' (e.g. Quitkin *et al*., 1972; Swendsen *et al*., 1998, 2000; Preisig *et al*., 2001) suggests that the pharmacological and/or psychological effects of alcohol reduce the aversive anxiety symptoms, thereby increasing persistent and escalating use via negative reinforcement (e.g. Brady and Lydiard, 1993). According to LaBounty *et al*. (1992), a self-medicating style of drinking, appearing before or after alcoholism is established, can contribute to a relapse to problem drinking after a period of abstinence among comorbid individuals. However, patients with anxiety symptoms who drink seem to be especially vulnerable to the development of withdrawal symptomatology (Kushner *et al*., 2000). This may be explained by an additional mechanism such as the notable overlap in the neuro-processess associated with anxiety symptoms and alcohol withdrawal states (e.g. γ-aminobutyric acid and noradrenaline transmission), which may influence the return to drinking (e.g. George *et al*., 1990). This phenomenon may explain why those patients with anxiety disorder are apparently vulnerable to entering the vicious feed-forward cycle of drinking-related anxiety reduction and induction. Anxiety symptoms, as a biopsychosocial consequence of chronic substance misuse and/or the withdrawal syndrome, have been discussed by George *et al*. (1990) and Schuckit (1996) for example.

A third view on the causality of the co-morbidity of alcoholism and anxiety suggests that both are caused by a shared third factor, such as non-biological environmental factors (e.g. a disruptive family environment or parental abuse or neglect), exposure to prenatal environmental factors (e.g. maternal alcohol use), genetic factors, or biological environmental risk factors (Geerlings and Lesch, 1999; Merikangas *et al*., 1996; Lesch *et al*., 2001).

According to Kushner *et al*. (2000) the interaction of the anxiogenic and anxiolytic process might best explain the aetiology of co-morbidity. The relief from anxiety immediately following drinking, along with the expectation that anxiety would increase if drinking were discontinued, appear alongside an overall worsening of anxiety as patients continued to drink. If anxiety increases pathological alcohol use, then active anxiety symptoms may increase the risk for relapse following alcoholism treatment. Alternatively, if pathological alcohol use increases anxiety symptoms, then successful alcoholism treatment may reduce or eliminate anxiety symptoms. Tomasson and Vaglum (1996) suggested that reducing clinical anxiety symptoms improves alcoholism treatment outcome and that ongoing problems with panic and anxiety predict relapse.

Summing up, our results show also that high anxiety as a stable trait, and personality traits, such as high NS and low HA, covering exploratory excitability, impulsiveness, extravagance, disorderliness and uninhibited optimism, predict relapse to uncontrolled drinking in male and female detoxified alcohol-dependent patients. This could have implications for additional treatments.

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