Correlates of Benzodiazepine Dependence in the Netherlands Study of Depression and Anxiety

Leonie Manthey
Marijke Lohbeck
Erik J. Giltay
Tineke van Veen
Frans G. Zitman
Brenda W.J.H. Penninx

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ABSTRACT

Aims: Benzodiazepines (BZDs) are effective on the short-term against anxiety and insomnia. However, some BZD users develop BZD dependence after a relatively short period of time. Therefore, we aimed to identify the risk factors of BZD dependence.

Design: An observational cohort study.

Setting: The Netherlands.

Participants: Four hundred one BZD users (13.5%) of the 2,981 participants of the Netherlands Study of Depression and Anxiety (NESDA) were included.

Measurements: Sociodemographic, physical, psychological, addiction related, and BZD use related characteristics were investigated as possible correlates of BZD dependence severity. Dependence severity was measured by the three subscales of the Benzodiazepine Self-Report Questionnaire, which are Problematic Use, Preoccupation, and Lack of compliance.

Findings: In multivariate analyses, Problematic Use was associated with more GP contacts in the past six months (β= 0.170, p=0.001) and severity of insomnia (β= 0.145, P=0.004). Preoccupation was related with anxiety severity (β= 0.194, P=0.001), antidepressant use (β= 0.197, P<0.001), alcohol dependence (β= 0.185, P<0.001), and a higher daily dosage of BZD (β= 0.160, P=0.001). Lack of compliance was associated with higher age (β= 0.122, P=0.03), unemployment (β= 0.105, P=0.04), insomnia (β= 0.129, P=0.01), antidepressant use (β= 0.148, P=0.002), and alcohol dependence (β= 0.108, P=0.02).

Conclusions: Insomnia, antidepressant use and alcohol dependence may increase the risk of BZD dependence among individuals who use BZDs.

INTRODUCTION

Benzodiazepines (BZDs) are effective on the short-term against anxiety and insomnia.[1] Long-term use is associated with the development of tolerance[2,3] even at therapeutic dosages.[4] Interestingly, some subjects cease BZD use after a relatively short period of time, while others do not,[5] possibly, due to the development of BZD dependence.[6] The identification of risk factors of dependence severity would allow physicians to prevent BZD dependence in some cases.

BZD dependence was found to be associated with sociodemographic factors (female sex,[7] lower age,[8] non-Dutch cultural origin,[8] lower education,[8] and retirement[8]), psychological and psychiatric factors (depression,[8-11] anxiety,[7-10] antidepressant use,[12] hostility,[8] less difficulties to obtain help for emotional problems,[7] and lower quality of life[9]), physical factors (somatization[11]), addiction related factors (treatment for dependence,[8] drug use[10]), and BZD use related factors (a high daily dosage,[8,12] long-term BZD use,[8,12] short half-life of BZDs,[8] and concomitant use of several BZDs[8]).

However, correlates identified in some studies were not significant in others, possibly due to the following reasons. First, previous studies reporting on BZD dependence used very different patient samples. The included patient samples consisted of community-dwelling seniors with a relatively low percentage of psychiatric diagnoses,[13] long-term BZD users who participated in a BZD reduction trial,[11] patients on buprenorphine maintenance treatment for opiate dependence,[9,14] psychiatric outpatients,[8] club drug users who also abused psychoactive prescription medication,[10] and subjects from addiction centers[13]. While in some studies a large percentage suffered from substance disorder[8] or psychiatric disorders[13], others excluded subjects with a substance abuse disorder or those who received treatment for psychiatric disorders[11]. Second, most studies were restricted to sociodemographic, psychological and BZD use-related correlates and thus did not include all important

variables in one multivariate model.[9,13] Third, the studies applied different definitions of BZD dependence or just investigated aspects of BZD dependence (dependence,[7,8,12] abuse or dependence,[9] addiction, withdrawal, craving[11]).[15] Most of the studies applied dichotomous (yes/no) definitions of dependence,[7,9] while the clinical expression of BZD dependence is better modeled using several subscales[15] and stages of severity[14].

The Benzodiazepine Dependence Self-Report Questionnaire (Bendep-SRQ) has been developed to take severity and subscales into account. The Bendep-SRQ describes severity of BZD dependence by means of three subscales: (awareness of the own) problematic use, preoccupation (with the availability of BZDs), and lack of compliance (with the therapeutic regime).[16] These subscales reflect psychological, physiological, and social aspects of BZD dependence and have been validated by psychiatrists, general practitioners, and self-help patients.[16]

Only one previous study has investigated the correlates of these three subscales of dependence severity.[8] Lower age, depressive disorder, duration and dosage of BZD use were associated with higher scores on problematic use.[8] Anxiety disorder, a short half-life of the BZD and a longer duration of BZD use were associated with more preoccupation.[8] Lower age, retirement, duration of BZD use and a higher dosage were associated with more lack of compliance.[8] Being an outpatient in a substance addiction center was associated with higher scores on all three subscales.[8] However, this study did not examine the impact of some potential physical (chronic illnesses, pain, and GP visits) and addiction-related (alcohol dependence, and tobacco dependence) variables although they might very well be of importance.

This study aimed to determine the independent cross-sectional correlates of BZD dependence severity. We included sociodemographic, psychological, physical, addiction-related, and BZD use-related factors in an extensive multivariate model. We used three subscales of the Bendep-SRQ to measure severity of BZD dependence.[16-18]

MATERIALS AND METHODS

Subjects

Subjects participated in the baseline assessment of the Netherlands Study of Depression and Anxiety (NESDA), a longitudinal cohort study of 2981 adults aged 18-65 years. NESDA was designed to be representative of individuals with depressive and/or anxiety disorders in different health care settings and developmental stages of illness. Subjects were recruited from the community, general practice and specialized mental health care institutions throughout the Netherlands. Primary care patients were recruited from 65 general practitioners by a three-stage screening procedure. A questionnaire was sent to a random sample of 23,750 patients to screen for affective and anxiety disorders. The screen-positives were approached for a phone interview to confirm the diagnoses. Finally, 743 participants with a six months diagnosis, 353 participants with a remitted diagnosis and 141 subjects with subshreshold symptoms were included. Additionally, 373 participants with a screen-negative score participated as control group.[19,20] Regarding specialized mental health care, each newly enrolled patient at the participating outpatient clinics participated in a standardized intake. The clinic staff submitted 1,597 patients with primary depressive or anxiety disorder for inclusion. After exclusion of subjects who did not fulfill inclusion criteria, could not be reached or refused participation, a final sample of 807 subjects remained. At the baseline assessment, all subjects completed a medical exam, an in-person interview, and several self-report questionnaires. The study protocol was approved by the ethical review boards of all participating centers, and all subjects gave written informed consent.[19] A more detailed description can be found in Penninx et al. (2008).[19]

To determine the independent predictors of BZD dependence severity, only BZD users (n=462) were included. As dependence severity was the outcome variable of our analyses, BZD users who had not completed the Bendep-SRQ were excluded (n=61). BZD users who had

filled in the Bendep-SRQ did not differ significantly from those who had not filled in the questionnaire in terms of gender, age, education, and severity of insomnia, anxiety and depression. After exclusion, 401 subjects were available for analysis.

Assessment of BZD Use and BZD Dependence

BZD use in the month prior to the baseline interview was registered by observation of drug-containers brought to the interview (73.6%) or by self-report. Information was collected about name, dose, frequency, number of tablets, and duration of BZD use. The medication was coded according to the Anatomical Therapeutic Code/Defined Daily Dose (ATC/DDD) system developed by the World Health Organization (WHO) collaborating Centre for Drug Statistics Methodology.[21] The Mean Daily Dose was calculated by dividing individual daily doses (in milligrams) of BZDs by the DDD for the particular BZD.[22] For BZDs other than diazepam, an equivalent daily dose was calculated.[23] Dosages were summed when more than one kind of BZD was used. Kinds of BZDs were subdivided into short acting and long acting types of BZDs. Duration of use was recorded in months.[22]

In order to assess the severity of dependence on BZDs, the Bendep-SRQ was used.[18] This questionnaire showed good validity in outpatient settings, and has been used to measure BZD dependence in many previous research studies.[16-18,22] We measured three subscales of the Bendep-SRQ reflecting separate subscales of dependence (5 items each): 1) awareness of problematic use, 2) preoccupation with the availability of BZDs, and 3) lack of compliance with the therapeutic regimen. All subscales showed good reliability and validity and convincingly met the requirements of the Rasch model.[18] Each item of the Bendep-SRQ had 5 possible answers ranging from 1'this is totally not true for me' to 5 'this is totally true for me'. To derive a total score for each 5-item subscale, scores for the individual items per subscale were summed yielding a score ranging from 5 to 25.

Vulnerability Factors of BZD Dependence

Five groups of vulnerability factors were assessed based on previous literature concerning BZD dependence: 1) sociodemographic factors, 2) psychological factors, 3) physical factors, 4) addiction related factors, and 5) factors related to the use of BZDs.[7-9,11-12] Detailed information about these variables and their assessment can be found elsewhere.[19]

In short, sociodemographic factors were reported during the baseline interview and included gender, age, Northern European ancestry (yes, no), education (in years), employment status (employed, unemployed, pension/housewife), and partner status (current partner, no partner, divorced/widowed).

Psychological factors included the severity of the depression and anxiety symptoms, insomnia, personality traits, mastery, and antidepressant use (yes/no). Severity of depressive symptoms was measured by the cognitive/mood scale of the Inventory of Depressive Symptomatology Self Report (IDS-SR), a 30-item self report scale.[24] The severity of generalized anxiety and panic symptoms at baseline was assessed with the Beck Anxiety Inventory (BAI).[25] The presence of insomnia was determined using the Insomnia Rating Scale (IRS).[26] Personality traits were assessed with the Neuroticism Extraversion Openness-Five Factor Inventory (NEO-FFI).[27] Locus of control or mastery was assessed with the 5-item version of the Pearlin Mastery Scale.[28] Antidepressant use was reported during the interview and classified as selective serotonin reuptake inhibitors (SSRIs; ATC codes N06AB02-N06AB10), tricyclic antidepressants (TCAs; ATC codes N06AA01-N06AA23), and other antidepressants including tetracyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and trazodone (ATC codes N06AX05, N06AX11, N06AX16, and N06AX21).

Physical factors included the number of chronic somatic illnesses, medical consumption in the last 6 months and level of pain. An inventory of chronic somatic diseases was made by detailed questions on the presence of chronic illnesses such as chronic lung disease and

heart condition. Medical consumption was defined as the number of GP consultations in the six months prior to the baseline interview, as assessed with the Perceived Need for Care Questionnaire (PNCQ).[29] Pain complaints were measured with the Chronic Graded Pain Scale (consisting of pain intensity and disability).[30]

Addiction related vulnerability factors were the level of dependence on nicotine, a life time diagnosis of alcohol abuse or alcohol dependence, and illicit drug use. Illicit drug use in the month before the baseline interview (cannabis, ecstasy, speed, cocaine, heroin, LSD) was reported during the baseline interview. Nicotine dependence among smoking subjects was measured with the Fagerström questionnaire.[31] Life time diagnoses of alcohol abuse and dependence according to DSM-IV criteria were assessed by the Composite International Diagnostic Interview (CIDI, life time version 2.1).[32]

Statistical Analyses

Sample characteristics and characteristics of BZD use were expressed by percentages, means (and standard deviations) for positively skewed variables or medians (and interquartile ranges) for non-normally distributed variables.

The non-normally distributed Bendep subscale 'lack of compliance' was naturally log transformed for regression analyses. Separate univariate linear regression analyses were carried out to identify the determinants of 1) problematic BZD use 2) preoccupation with availability of BZDs and 3) lack of compliance to the therapeutic regime. All independent variables with $P<0.10$ in univariate analyses were entered into the multivariate regression analyses in order to determine the independent correlates of BZD dependence severity as measured with the three subscales. The above mentioned sociodemographic, psychological, physical, addiction related, and BZD use related vulnerability factors were entered as possible correlates of BZD dependence. All variables with $P<0.05$ in the multivariate models were considered statistically significant. The frequent

BZD users (> 50% of all days in the past month, n=201) were analyzed separately in sensitivity analyses. All analyses were conducted with SPSS 17.0 for Windows.

RESULTS

Characteristics of the Study Group

Of the investigated 401 BZD users, 158 subjects used BZDs on a daily basis (39.4%), 43 (10.7%) used BZDs more than 50% of all days in the past month, 88 subjects (21.9%) used BZDs less than 50% of all days in the past month, and 112 (27.9%) used BZDs when needed. The sociodemographic-, psychological-, physical-, and addiction-related characteristics of the 401 BZD users are shown in Table 1. BZD users were mainly female (69.6%), had a mean age of 46.0 years, and often had a current partner (62.8%). Pure depression disorder (15.5%), pure anxiety disorder (18.7%) or comorbid depression and anxiety disorder (51.4%) were commonly present and 53.4% of the BZD users also used antidepressants. Approximately one fourth of the BZD users had a lifetime diagnosis of either alcohol dependence or abuse. As for the three subscales of BZD dependence severity, the BZD users scored highest on the Bendep-SRQ subscale preoccupation, followed by problematic use and lack of compliance. The mean duration of BZD use was 24.0 months and the average daily dose was 2.8 mg diazepam equivalents per day.

Problematic Use

Univariate and multivariate correlates of problematic use are shown in Table 2. In multivariate analyses, more GP contacts in the past six months (β= 0.170; P=0.001), severity of insomnia (β= 0.145; P=0.004), and antidepressant use (β= 0.108; P=0.02) were associated with more problematic use. There were no independent sociodemographic and addiction related characteristics of problematic use. When analyses were repeated in frequent BZD users only (data not shown), the betas of

GP contacts in the last six months (β=0.266) and more severe insomnia remained comparable (β=0.138). Only the beta of antidepressant use decreased in strength in the frequent user group only.

Preoccupation

In multivariate analyses (Table 3), higher scores on the BAI (β= 0.194; P=0.001), antidepressant use (β= 0.197; P≤0.001), alcohol dependence (β= 0.185; P≤0.001), and a higher daily dosage of BZDs (β= 0.160; P=0.001) were associated with higher scores on preoccupation. No sociodemographic and physical characteristics were associated with preoccupation. When frequent users were analyzed separately, severity of anxiety (β =0.250) and alcohol dependence (β =0.217) remained important correlates. Antidepressant use (β =0.061) and dosage of BZD use (β =0.099) lost relevance in the frequent user group. Severity of depression was negatively associated with preoccupation in the frequent users only (β =-0.272), but not in the whole group (β =-0.054).

Lack of Compliance

In the multivariate model (Table 4), higher age (β= 0.122; P=0.03), unemployment due to sickness or disability (β= 0.105; P=0.04), more severe insomnia (β= 0.129; P=0.01), antidepressant use (β= 0.148; P=0.002), and alcohol dependence (β= 0.108; P=0.02) were associated with more lack of compliance. No physical characteristics were associated with of lack of compliance. When frequent BZD users were analyzed separately, the betas of unemployment (β=0.186), severity of insomnia (β=0.140), alcohol dependence (β=0.118), and antidepressant use (β=0.111) remained comparable while the beta of age decreased. In contrast, mastery (β=-0.240) and pain (β=0.231) had higher betas in the frequent user group only than in the whole group.

TABLE 1. Characteristics of 401 BZD Users and their BZD Use

Sociodemographic characteristics	
Sex (female, %)	69.6
Age in years	46.0 (11.6)
Partner status (%)	
Current partner	62.8
No partner	20.9
Widowed/divorced	16.2
Employment status (%)	
Employed	39.7
Unemployed	56.1
Pension/housewife	4.2
Education level in years	11.0 (9.0 – 15.0)
North European ancestry (%)	95.3
Physical vulnerability factors	
Number medical contacts 6 months	3.3 (2.0 – 5.0)
Number chronic illnesses	2.0 (1.0 – 4.0)
Severity of pain	2.0 (1.0 – 3.0)
Psychological vulnerability factors	
One year diagnosis (%)	
MDD only	15.5
Anxiety only	18.7
Comorbid disorder	51.4
Mastery Scale	15.0 (12.0 – 18.0)
BAI Questionnaire	20.0 (10.0 – 28.0)
Insomnia Rating Scale	10.0 (8.0 – 15.0)
IDS Questionnaire	12.0 (7.0 – 16.0)
Antidepressant use (past month, %)	53.4
Personality Characteristics	
Neuroticism	28.9 (7.8)
Extraversion	21.9 (6.7)
Openness	25.1 (6.1)
Agreeableness	31.4 (5.5)
Conscientiousness	28.6 (6.0)
Addiction related factors	
Fagerström Questionnaire	3.0 (0.0 – 3.9)
Alcohol dependence (%)	19.7
Alcohol abuse (%)	9.0
Drug use past month (%)	6.2
Bendep-SRQ Subscales	
Problematic use	9.6 (3.1)
Preoccupation	13.0 (4.2)
Lack of compliance	7.0 (5.0 – 9.0)
Characteristics of BZD use	
Type of BZD	
Short acting (% t1/2 < 24h)	79.6
Long acting (% t1/2 > 24h)	20.4
Daily BZD use (%)	39.4
Daily dose (mg/day)*	2.8 (0.7 – 6.0)
Duration of use (months)	24.0(5.0 – 96.0)
Most frequently used BZDs (%)	
Diazepam	15.2
Oxazepam	46.6
Alprazolam	6.0
Temazepam	14.2
Lorazepam	4.5
Zopiclone	2.7

BZD indicates benzodiazepine; GP indicates general practitioner; IDS indicates Inventory of Depressive Symptomatology; BAI indicates Beck Anxiety Questionnaire; MDD indicates Major Depressive Disorder. Bendep-SRQ indicates Bendep Self-Report-Questionnaire. Means (standard deviation) are given for age, personality characteristics, Problematic Use and Preoccupation. Medians (interquartile range) are given for education level, medical consumption, number of chronic illnesses, pain, mastery, IRS, BAI, IDS, Fagerström, Lack of Compliance, duration of BZD use, and daily BZD dose as these values are not normally distributed. Percentages are given for categorical variables. *Expressed as diazepam equivalents

TABLE 2. Univariate and multivariate Correlates of Problematic Use in 401 BZD Users

	Univariate associations		**Multivariate associations**	
	β	P*	β	P**
Sociodemographic characteristics				
Sex (female)	0.010	0.84		
Age (years)	-0.046	0.36		
Partner status				
No partner	0.010	0.85		
Widowed/divorced	0.050	0.32		
Employment status				
Unemployed/sickness/disabled	0.201	**<0.001**	0.064	0.21
Pension/housewife	-0.084	0.09	0.026	0.60
Education level (years)	-0.196	**<0.001**	-0.088	0.07
Northern European ancestry	-0.070	0.16		
Physical vulnerability factors				
GP contacts last 6 months	0.294	**<0.001**	0.170	**0.001**
Chronic illnesses	0.145	**0.004**	0.018	0.72
Pain	0.226	**<0.001**	0.006	0.91
Psychological vulnerability factors				
Mastery Scale	-0.199	**<0.001**	-0.081	0.12
BAI Questionnaire	0.315	**<0.001**	0.088	0.14
Insomnia Rating Scale	0.227	**<0.001**	0.145	**0.004**
IDS Questionnaire	0.311	**<0.001**	0.062	0.40
Antidepressant use	0.177	**<0.001**	0.108	**0.02**
Personality Characteristics				
Neuroticism	0.269	**<0.001**	0.074	0.27
Extraversion	-0.096	0.05	0.107	0.06
Openness	-0.105	**0.04**	-0.028	0.56
Agreeableness	-0.106	**0.04**	-0.004	0.94
Conscientiousness	-0.112	**0.03**	0.025	0.64
Addiction related vulnerability factors				
Fagerström Questionnaire	0.123	**0.01**	0.032	0.51
Alcohol dependence	0.108	**0.03**	0.076	0.10
Alcohol abuse	-0.007	0.89		
Drug use past month	0.033	0.51		
Characteristics of BZD use				
Long half life	0.046	0.36		
Duration of use (in months)	0.018	0.72		
Daily Dosage in diazepam equivalents	0.183	**<0.001**	0.082	0.09

BZD indicates benzodiazepine; GP indicates general practitioner; BAI indicates Beck Anxiety Inventory; IDS indicates Inventory of Depressive Symptomatology. All correlates with P<0.10 are included in multivariate analyses. Correlates with P<0.05 in multivariate analyses were considered as statistically significant. *P values are obtained by univariate regression analyses. ** P values are obtained by multivariate regression analyses.

TABLE 3. Univariate and multivariate Correlates of Preoccupation in 401 BZD Users

	Univariate associations		**Multivariate associations**	
	β	P*	β	P**
Sociodemographic characteristics				
Sex (female)	-0.033	0.51		
Age (years)	0.067	0.18		
Partner status				
No partner	-0.030	0.55		
Widowed/divorced	0.016	0.74		
Employment status				
Unemployed/sickness/disabled	0.148	**0.003**	0.041	0.41
Pension/housewife	-0.065	0.20	0.034	0.48
Education level in years	-0.102	**0.04**	-0.045	0.34
Northern European ancestry	-0.009	0.85		
Physical vulnerability factors				
GP contacts last 6 months	0.151	**0.002**	0.069	0.16
Chronic illnesses	0.047	0.35		
Pain	0.103	**0.04**	-0.056	0.28
Psychological vulnerability factors				
Mastery Scale	-0.163	**0.001**	-0.044	0.38
BAI Questionnaire	0.301	**<0.001**	0.194	**0.001**
Insomnia Rating Scale	0.044	0.38		
IDS Questionnaire	0.236	**<0.001**	-0.054	0.45
Antidepressant use	0.272	**<0.001**	0.197	**<0.001**
Personality Characteristics				
Neuroticism	0.245	**<0.001**	0.090	0.17
Extraversion	-0.158	**0.002**	0.004	0.94
Openness	-0.035	0.48		
Agreeableness	-0.054	0.28		
Conscientiousness	-0.116	**0.02**	0.035	0.51
Addiction related vulnerability factors				
Fagerström Questionnaire	0.074	0.14		
Alcohol dependence	0.230	**<0.001**	0.185	**<0.001**
Alcohol abuse	-0.062	0.22		
Drug use past month	-0.036	0.47		
Characteristics of BZD use				
Long half life	-0.001	0.99		
Duration of use (in months)	0.075	0.13		
Daily Dosage in diazepam equivalents	0.267	**<0.001**	0.160	**0.001**

BZD indicates benzodiazepine; GP indicates general practitioner; BAI indicates Beck Anxiety Inventory; IDS indicates Inventory of Depressive Symptomatology. All correlates with P<0.10 are included in multivariate analyses. Correlates with P<0.05 in multivariate analyses were considered as statistically significant. *P values are obtained by univariate regression analyses. ** P values are obtained by multivariate regression analyses.

TABLE 4. Univariate and multivariate Correlates of Lack of Compliance in 401 BZD Users

	Univariate associations		**Multivariate associations**	
	β	P*	β	P**
Sociodemographic characteristics				
Sex (female)	-0.003	0.95		
Age (years)	0.171	**0.001**	0.122	**0.03**
Partner status				
No partner	-0.049	0.32	-0.005	0.92
Widowed/divorced	0.088	0.08	0.023	0.64
Employment status				
Unemployed/sickness/disabled	0.234	**<0.001**	0.105	**0.04**
Pension/housewife	-0.014	0.78	0.042	0.40
Education level in years	-0.204	**<0.001**	-0.078	0.12
Northern European ancestry	0.059	0.24		
Physical vulnerability factors				
GP contacts last 6 months	0.149	**0.003**	0.013	0.80
Chronic illnesses	0.183	**<0.001**	0.022	0.67
Pain	0.222	**0.003**	0.104	0.06
Psychological vulnerability factors				
Mastery Scale	-0.187	**<0.001**	-0.086	0.10
BAI Questionnaire	0.190	**<0.001**	-0.064	0.29
Insomnia Rating Scale	0.229	**<0.001**	0.129	**0.01**
IDS Questionnaire	0.298	**<0.001**	0.136	0.07
Antidepressant use	0.199	**<0.001**	0.148	**0.002**
Personality Characteristics				
Neuroticism	0.205	**<0.001**	0.047	0.50
Extraversion	-0.170	**0.001**	0.052	0.36
Openness	-0.153	**0.002**	-0.077	0.11
Agreeableness	-0.099	**0.048**	0.022	0.66
Conscientiousness	-0.137	**0.006**	0.002	0.97
Addiction related vulnerability factors				
Fagerström Questionnaire	0.108	**0.03**	0.028	0.56
Alcohol dependence	0.143	**0.004**	0.108	**0.02**
Alcohol abuse	-0.057	0.26		
Drug use past month	0.041	0.42		
Characteristics of BZD use				
Long half life	0.120	**0.02**	0.055	0.24
Duration of use (in months)	0.131	**0.009**	0.069	0.17
Daily Dosage in diazepam equivalents	0.205	**<0.001**	0.054	0.28

BZD indicates benzodiazepine; GP indicates general practitioner; BAI indicates Beck Anxiety Inventory; IDS indicates Inventory of Depressive Symptomatology. All correlates with P<0.10 are included in multivariate analyses. Correlates with P<0.05 in multivariate analyses were considered as statistically significant. *P values are obtained by univariate regression analyses. ** P values are obtained by multivariate regression analyses.

DISCUSSION

This study investigated a large set of potential correlates of problematic use, preoccupation, and lack of compliance as indicators of BZD dependence in 401 BZD users. Problematic use was independently associated with more GP contacts, antidepressant use and higher severity of insomnia. Preoccupation was independently associated with anxiety severity, antidepressant use, alcohol dependence, and a higher daily dosage of BZDs. Lack of compliance was independently associated with higher age, unemployment, insomnia, antidepressant use, and alcohol dependence. The following paragraphs will discuss each of the three subscales separately.

High scores on problematic use implied that users were aware of the negative impact of BZDs on their lives, thought about discontinuing, and felt BZDs became less effective in symptom reduction.[16] It is noteworthy that severe insomnia was associated with higher scores on problematic use although BZDs are actually prescribed to lessen insomnia. Further, it is remarkable that subjects were aware of the apparent ineffectiveness of BZDs as well as of their problematic use, but were unable to discontinue BZDs, possibly due to the fear that symptoms might worsen.[4,33-34] GP visits as a correlate of problematic use is in line with previous research reporting a negative association between embarrassment to obtain help and BZD dependence.[13] Subjects who visit their GPs more often may be more likely to become dependent on BZDs (as more BZD prescriptions are issued). With respect to awareness of problematic use, it may also indicate that GPs call their patients' attention on the problems associated with their BZD use. Alternatively, subjects may have been sicker, more in need of GP consultations, and thus more vulnerable to problematic use.

Subjects with high scores on preoccupation with BZDs became nervous when they did not carry their drugs with them and were generally very concerned with BZDs.[16] The association between anxiety and preoccupation was in line with previous research[8,35] and may be due

to a partial conceptual overlap between these constructs. Additionally, subjects with mental disorders were previously shown to self-medicate their problems and subsequently become dependent.[36] The association between preoccupation and antidepressant use is in line with an earlier reported association between depression and BZD craving.[11] It supports the assumption that the presence of negative mood states appears sufficient to elicit the desire for substance (ab)use of e.g. alcohol.[37] Alcohol dependence was also an expected correlate of BZD dependence[8,38] as both substances influence the same gamma-aminobutric acid alpha receptor and cause a dampening of nervous system activity. Subjects may use either substance prior to stressful situations in order to feel calmer. Alternatively, BZDs might have been administered to relieve the withdrawal effects of alcohol and vice versa[39,40] or to increase sedation[41].

Subjects who scored high on lack of compliance with the therapeutic regime took more BZDs than prescribed, tried to renew prescriptions earlier than agreed on, and sometimes even falsified prescriptions.[16] Unemployed and older subjects, who form a vulnerable group in general, had higher scores on lack of compliance. This was roughly in line with previous research.[8,42] It may indicate that for these vulnerable subjects adhering to social norms such as a therapeutic regime become less important. Insomnia being a correlate of lack of compliance possibly pointed toward tolerance development and the resulting perceived need to administer more BZDs (than prescribed) to relieve the insomnia. The concomitant use of antidepressants, BZDs, and alcohol possibly indicated more severe psychopathology and stress vulnerability. Polydrug use might have reduced the threshold to take medication so that prescription constraints were taken less seriously and lack of compliance to therapeutic regimes becomes more likely.[41]

Kan et al. identified a number of correlates of BZD dependence which did not appear to be of importance in the NESDA sample (e.g. duration of BZD use and half-life of BZD).[8] These inconsistencies may be due to the inclusion of different correlates of BZD dependence. Further,

Kan et al. included part of their sample from outpatient addiction centers and the average daily dosage of BZDs in his sample was much higher than in NESDA (10mg vs. 2.8mg of diazepam equivalents, respectively) which might put subjects at increased risk to develop BZD dependence.[8]

In general, it is interesting that mainly psychological, addiction- and BZD use related characteristics predicted BZD dependence. Insomnia, antidepressant use and alcohol dependence predicted BZD dependence severity on two or more severity subscales. Other risk factors which were significant on one subscale (i.e., BAI, alcohol dependence, daily dosage) were borderline significant on other subscales. Therefore, most of the found risk factors seemed to be rather general predictors of BZD dependence. However, there were small disparities across the three subscales. For example, only preoccupation was related to anxiety, only lack of compliance was related to age and unemployment, and only problematic use to GP contacts. Frequency of use by itself seems to be an important predictor of dependence development. This finding is not surprising and in line with previous research reporting that a high daily dosage increases the risk of BZD dependence.[8,12]

Subjects at risk of BZD dependence are in need of close monitoring as they are also vulnerable to the development of concomitant mental disorders and substance abuse. They may benefit from psychotherapy and counseling to make them more resilient and possibly prevent BZD dependence. Further, the therapeutic effectiveness of BZDs should be monitored closely and weighted against the disadvantages, especially in those at risk of BZD dependence. If psychopathology does not improve with treatment, it is recommended to discontinue BZD use and switch to alternative ([non-] pharmacological) treatment options to prevent ineffective long term BZD use.

The present study had some limitations. The observational and cross-sectional design did not allow causal inferences on whether the correlates preceded severity of BZD dependence or vice versa. Our results cannot be generalized to very specific BZD user populations (such as

drug addicts and mentally healthy subjects who only receive BZDs for non-psychiatric disorders such as pain) but only to outpatients using relatively low-dosage of BZDs who mostly suffer from anxiety and insomnia (which are the main indications for BZD use). Further, in the light of the number of correlates tested, multiple testing may have caused type I errors. Despite these limitations, our study had important strengths. We conducted a multivariate analysis across a comprehensive set of possible determinants of BZD dependence so that we were able to identify the independent correlates of BZD dependence severity. In addition, we investigated a large study sample composed of subjects with a wide range of psychopathology representative of the average BZD user. The use of continuous Bendep-SRQ sumscores instead of dichotomous ones allowed us to measure the full variability of the phenotype and detect small differences between subjects and the more subtle associations.

In conclusion, subjects with insomnia, antidepressant use, and alcohol dependence were at highest risk to develop more severe BZD dependence. As concomitant psychopathology and substance dependence may severely compromise these subjects' quality of life, close monitoring and more appropriate symptom treatment is needed.

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