Correlates of (inappropriate) Benzodiazepine Use: the Netherlands Study of Depression and Anxiety (NESDA)

Leonie Manthey
Tineke van Veen
Erik J. Giltay
José E. Stoop
Arie Knuistingh-Neven
Brenda W.J.H. Penninx
Frans G. Zitman

British Journal of Clinical Psychopharmacology 2011, 71 (2): 263 - 272

ABSTRACT

Aim: Results on correlates of benzodiazepine (BZD) use in general and inappropriate use were inconsistent and mostly univariate. The relative importance of sociodemographic, psychological and physical correlates has never been investigated in a comprehensive, multivariate model.

Methods: We included 429 BZD users and 2423 non-users from the Netherlands Study of Depression and Anxiety (NESDA) in order to investigate sociodemographic, psychological and physical correlates of BZD use and inappropriate use by logistic and linear regression analyses.

Results: BZDs were used by a considerable proportion of the 2852 NESDA participants (15.0%). BZD use was independently associated with older age, singleness, unemployment, treatment in secondary care, higher medical consumption, (more severe) anxiety, depression (OR[95%CI]=1.95[1.29,2.93]), comorbidity, insomnia, SSRI (OR[95%CI]=2.05[1.55,2.70]), TCA, and other antidepressant (OR[95% CI]=2.44[1.64,3.62]) use. Overall, BZD use was rarely in accordance with all guidelines, mainly because most users (82.5%) exceeded the recommended duration of safe use. Inappropriate use was independently associated with older age (β = 0.130) and chronic illnesses (β = 0.120). Higher scores on agreeableness were associated with less inappropriate use.

Conclusions*:* Mentally or physically vulnerable subjects were most likely to use BZDs. The most vulnerable (i.e. old and physically ill) BZD users were at highest risk of inappropriate BZD use. Without further evidence of BZDs effectiveness in long-term use, caution in initiating BZD prescriptions is recommended, particularly when patients are chronically ill and old, as those are most likely to display inappropriate use.

INTRODUCTION

Benzodiazepines (BZDs) are commonly prescribed as a treatment of anxiety and insomnia.[2-5] Remarkably, BZDs are also inappropriately used for pain,[6] somatic illnesses,[1] and less specific stress responses.[7,8] Although there is still controversy about the potential for abuse, dependence, withdrawal symptoms, and side effect, prevalence rates of BZD use are high and vary between 7.5% and 21.3% across countries.[9-12] Due to these high prevalence rates, it is informative to obtain a profile of the average BZD user. Specific subject characteristics such as sociodemographic factors (female sex,[5,12-15] older age,[3,5,12-16] lower education,[14] and unemployment[12,13,15]), psychological characteristics (worse mental health,[3,13,15-17] antidepressant use,[13,18] and elevated neuroticism[14,15,17]) and physical health factors (chronic illnesses or other physical health problems,[1,13-18] higher medical consumption,[18] and pain complaints[6]) were found to be associated with BZD use in previous studies. A number of these variables,[5,12,13] but not all,[14,15,17] were identified as important correlates of BZD use in the majority of studies. Several studies did not look at the determinants independently by using a multivariate analysis[3,5,14,17,18] and no joint investigation of all determinants has been conducted yet.

When BZDs are used as indicated, i.e. at standard therapeutic doses, during a short time period, and only one type of BZD at a time, treatment is usually without strong side effects.[19] Inappropriate BZD use is accompanied by adverse health consequences including cognitive impairment, risk of falling, traffic accidents, and dependence.[6,20-23] Further, there is little evidence for the effectiveness of BZDs during chronic use.[24] Therefore, several national and international guidelines were formed that – although showing some differences– all recommended a conservative practice of prescription, including short-term use.[25-27] However, more than 20 years after the notion that long-term BZD use should be discouraged, still more than 50% of current BZD users are chronic users (i.e., using BZDs for more than 3 months).[12,28,29] To prevent

inappropriate use, it is important to determine which users become inappropriate users. To date, the determinants of inappropriate use have not been investigated. Only the determinants of long-term use have been studied, yet with inconsistent results and without considering the other aspects of inappropriate use (i.e., dosage and number of BZD types used). In those studies, sex,[29-31] age,[28-33] education,[32] psychopathology,[32-34] physical health,[30,33,34] pain complaints,[34] daily BZD use,[28] use of higher potency BZDs,[31] and antidepressants[33] were identified as correlates of long-term BZD use.

To the best of our knowledge, we are the first study to investigate the relative importance of a comprehensive set of potential correlates of BZD use and inappropriate use in a study among 2852 subjects at various stages of psychopathology participating in the Netherlands Study of Depression and Anxiety (NESDA). We first explored the sociodemographic, psychological and physical correlates of BZD use. Second, we investigated (the correlates of) inappropriate use according to international guidelines.[25-27]

MATERIALS AND METHODS

Subjects

Subjects participated in the baseline assessment of the Netherlands Study of Depression and Anxiety (NESDA), an 8-year longitudinal cohort study of 2981 respondents aged 18 to 65 years.[35] NESDA was designed to be representative of individuals with depressive and/or anxiety disorders in different health care settings and developmental stages of illness.[35] Psychiatric status did not seem to be predictive of the initial (non)-response in the NESDA study. (Non)-response was driven by age and sex, i.e. older women more often participated in the NESDA study and young men less often.[35] Subjects were recruited from the community, general practice and specialized mental health care institutions throughout the Netherlands. They completed a medical exam, an in-person interview,

and several self-report questionnaires. The study protocol was approved by the Ethical Review Board of each participating centre and all subjects signed an informed consent at the baseline assessment.

We excluded subjects with one or more missing values on BZD use, inappropriate use, sociodemographic, psychological or physical characteristics (n=94). An exception was made for missing values on the Insomnia Rating Scale (IRS) where mean imputation was used due to the high number of missings (n=300). We also excluded subjects with epilepsy (n=29), as epilepsy is an indication that justifies prolonged BZD use.[36]

To obtain an indication of the main correlates of BZD use (aim [1]), two groups were defined: subjects who reported BZD use in the month prior to the baseline interview ('BZD users', n=429) and those reporting no use of BZDs in the last month ('non-users', n=2423). For the investigation of appropriateness of BZD use (aim [2]) only BZD users were considered and further categorized according to appropriateness of BZD use.

Benzodiazepine Use

Two indicators of BZD use were investigated: BZD use and appropriateness of BZD use.

BZD use during the month prior to baseline interview was registered by observation of drug containers brought to the interview (in 73.4% of cases) or self-report (in 26.6% of cases). Information was collected about name, dose, number of tablets, and duration of BZD use. 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. BZDs were classified as ATC-coded groups N05BA, N05CD, N05CG, and N03AE01. The so called "Z-drugs", of which in the Netherlands only zopiclone and zolpidem (ATC code N05CF) are available, were also included in our analyses, as studies on long-term adverse effects,

withdrawal and tolerance development for these drugs are still lacking. The daily BZD dose was computed according to the coding system of the ATC and DDD system.[37] The Mean Daily Dose was calculated by dividing individual daily doses (in mg) of BZDs by the DDD for the particular BZD.[38] For patients using BZDs other than diazepam, an equivalent daily dose was calculated with the conversion tables commonly used by general practitioners' (GPs)[39] and 10 mg of diazepam were regarded equivalent to 1 mg alprazolam, 10 mg bromazepam, 0.25 mg brotizolam, 20mg clobazam, 20 mg chlordiazepoxide, 13.3 mg clorazepate, 8 mg clonazepam, 30 mg flurazepam, 1 mg loprazolam, 2 mg lorazepam, 1 mg lormetazepam, 7.5 mg midazolam, 10 mg nitrazepam, 33 mg oxazepam, 20 mg prazepam, 20 mg temazepam, 20 mg zolpidem and 13 mg zopiclone. Dosages were summed when more than one BZD was used. Types of BZDs were subdivided into short acting ($t_{1/2}$ < 24h) and long acting ($t_{1/2}$ ≥ 24h) BZDs. Duration of use was categorized as short-term (≤ 3 months) or long-term (> 3 months). The number of different types of BZDs used was categorized into 1, 2, or 3. BZDs were further divided into anxiolytics (ATC code N05BA, n=263) and hypnotics (ATC codes N05CD and N05CF, n=147).

Appropriateness of use was based on the Dutch practice guidelines for anxiety and insomnia[26,27] and the British *National Institute of Health and Clinical Excellence* treatment guidelines for general practitioners.[25] The following criteria for appropriate use were derived:

1. mean daily dosage ≤ DDD as defined by the WHO
2. duration of benzodiazepine use ≤ 3 months in case of no concomitant antidepressant (AD) use and ≤ 2 months in case of concomitant AD use
3. only one type of BZDs is used at a time

Based on the number of appropriateness criteria not met by a subject, an inappropriateness score (range 0 – 3) was calculated. An inappropriateness score of 0 indicated that a subject met all three appropriateness criteria (i.e. appropriate use) whereas an inappropriateness score of 3 indicated

that none of the appropriateness criteria was met (i.e. highly inappropriate use).

Demographic, Psychological and Physical Characteristics

Based on previous studies, various potential correlates of BZD use and appropriateness of BZD use were included and grouped into: sociodemographic characteristics (age, gender, education, marital status, and work status), psychological characteristics (current psychopathology, health care setting, severity of anxiety or depression symptoms, insomnia, antidepressant use, and personality traits) and physical characteristics (number of chronic diseases, medical consumption; pain complaints, and smoking).[5,12-15,29,32-34,40]

Sociodemographic characteristics- Gender, age, education level (in years), work status (employed vs. unemployed), and partner status (living with partner vs. single) were reported in the baseline interview.

Psychological characteristics- In NESDA, depressive (dysthymia or Major Depressive Disorder, MDD) and anxiety (panic disorder with or without agoraphobia, generalized anxiety disorder or social phobia) diagnoses were measured by the Composite International Diagnostic Interview (CIDI, life time version 2.1), which classifies diagnoses according to the DSM-IV criteria. Current diagnoses were defined as those in the last year. The severity of generalized anxiety and panic symptoms were assessed with the Beck Anxiety Inventory (BAI).[41] The presence of insomnia was determined using the Insomnia Rating Scale (IRS).[42] The severity of depressive symptoms was measured by the cognitive/mood scale of the Inventory of Depressive Symptomatology Self Report (IDS-SR).[43] In order to avoid overlap with the BAI and IRS, we did not include the anxiety/arousal and sleep scales of the IDS-SR. So as to make the score of BAI, IDS-SR and IRS comparable, z-scores were calculated and z transformed values were used for regression analyses. Personality traits were assessed with the Neuroticism Extraversion Openness-Five Factor Inventory (NEO-FFI), a 60-item questionnaire measuring five personality

domains: neuroticism, extraversion, agreeableness, conscientiousness, and openness to experience.[44] Antidepressant use was reported during the interview. The ATC-coded groups N06AA, N06AB, N06AF, N06AX and N06AG were classified as antidepressants.

Physical characteristics - An inventory of somatic diseases was made by detailed questions of the presence of the following chronic illnesses: chronic lung disease, heart condition, diabetes mellitus, stroke, arthritis, rheumatism, cancer, hypertension, ulcer, intestinal problems, liver disease, chronic fatigue syndrome, allergy, thyroid gland, head injury or other injuries. Based on the number of chronic diseases a subject suffered from, a score ranging from 0 to 17 was calculated. Medical consumption was defined as the number of GP consultations in the six months prior to the interview, as assessed with the Perceived Need for Care Questionnaire (PNCQ).[45] Pain complaints were measured with the Chronic Graded Pain Scale and pain severity (consisting of pain intensity and disability) was summarized by the Chronic Pain Grade according to Korff et al., which is a score ranging from 0 to 4.[46] Smoking was reported during the interview.

Statistical Analyses

Sample characteristics and characteristics of BZD use were expressed by frequencies, means or medians, and compared using $\chi 2$ statistics (for categorical variables), analysis of variance (ANOVA, for normally distributed, continuous variables), and Mann-Whitney U-test (for non-normally distributed, continuous variables). Non-normally distributed values were naturally log transformed for regression analyses.

Univariate logistic and linear regression analyses were carried out to identify correlates of BZD use (vs. non-use as the reference category) and inappropriate use (inappropriateness score ranging from 0-3). Odds ratios with 95% confidence intervals (OR [95 % CI]) and standardized betas (β) were provided as outcome measures. All independent variables with $P < 0.10$ in univariate analyses were entered in the multivariate regression

models. The P value was set at $P < 0.10$ (instead of $P < 0.05$) in order to avoid missing important determinants of BZD use that do not reach significance in univariate analysis at $P < 0.05$ but will when correcting for possible confounders in multivariate analyses. The following variables were considered: [1] demographic variables: gender, age, education level, work status, and partner status, [2] psychological characteristics: current psychopathology, health care setting, severity of anxiety and depression symptoms, insomnia, antidepressant use, and personality traits, [3] physical characteristics: number of chronic diseases, medical consumption, pain complaints and smoking. The analysis was adjusted for sex and age. Significance in the multivariate model was inferred at $P <0.05$.

Finally, we compared anxiolytic and hypnotic users on possible characteristics of BZD use using $\chi 2$ statistics (for categorical variables), ANOVA (for normally distributed, continuous variables), and Mann-Whitney U-test (for non-normally distributed, continuous variables) to find out whether there would be group differences. Significance was inferred at $P < 0.05$. All analyses were conducted with SPSS 16.0 for Windows.

RESULTS

Characteristics of BZD Use

Of the 2852 subjects, 429 (15.0%) had used a BZD in the past month. Table 1 shows the sociodemographic, psychological, and physical characteristics of BZD users as compared to non-users.

BZD users were older (mean 46.3 vs. 41.2 years, $P<0.001$), more likely to be single (36.4% versus 29.6%, $P=0.005$), and more likely to be unemployed (51.7% vs. 28.4%, $P<0.001$). Further, BZD users displayed worse physical (3.0 vs. 2.0 medical consumption, $P<0.001$) and psychological health (BAI score of mean 20.0 vs. 8.0 respectively, $P<0.001$).

TABLE 1. Characteristics of Benzodiazepine (BZD) User Groups (n=2852)

	Non-Users n= 2423	BZD Users n=429	P-value
Sociodemographics			
Sex (% female)	66.1	68.1	0.43
Age (years)	41.2 (40.7 – 41.7)	46.3 (45.0 – 47.5)	<0.001
Partner status (% single)	29.6	36.4	0.005
Employment status (% not working)	28.4	51.7	<0.001
Education level (years)	12.0 (10.0 – 15.0)	11.0 (9.0 – 15.0)	<0.001
Treatment in secondary care (%)	24.2	49.0	<0.001
Physical health			
Medical consumption	2.0 (1.0 – 3.0)	3.0 (2.0 – 5.0)	<0.001
Chronic illnesses	1.8 (1.8 – 1.9)	2.5 (2.3 – 2.6)	<0.001
Pain	1.5 (1.5 – 1.6)	2.1 (2.0 – 2.2)	<0.001
Smoking (%)	28.9	24.2	0.05
Psychological Characteristics			
Current Diagnosis (%)			<0.001
MDD Only	15.1	17.5	
Anxiety Only	14.6	18.2	
Comorbid disorder	23.1	49.0	
IRS	8.0 (4.0 – 10.0)	10.0 (8.0 – 15.0)	<0.001
BAI	8.0 (3.0 – 16.0)	20.0 (10.0 – 28.0)	<0.001
IDS-SR Mood/Cognition Scale	5.0 (2.0 – 11.0)	12.0 (6.0 – 16.5)	<0.001
Antidepressant use (%, past month)			<0.001
SSRI	13.9	34.5	
TCA	2.1	6.1	
Others	4.2	14.0	
Personality Characteristics			
Neuroticism	23.5 (23.1 – 23.8)	28.7 (27.9 – 29.6)	<0.001
Extraversion	25.4 (25.1 – 25.7)	21.8 (21.1 – 22.4)	<0.001
Openness	26.4 (26.2 – 26.7)	25.3 (24.7 – 25.9)	<0.001
Agreeableness	31.9 (31.7 – 32.1)	31.2 (30.7 – 31.7)	0.02
Conscientiousness	30.5 (30.2 – 30.7)	28.8 (28.2 – 29.3)	<0.001

BAI indicates Beck's anxiety index; IDS-SR indicates Inventory of Depressive Symptomatology; IRS indicates Insomnia Rating Scale: MDD indicates Major Depressive Disorder; SSRI indicates Selective Serotonin Reuptake Inhibitor; TCA indicates Tricyclic Antidepressant. Means (95% confidence intervals) are given for age, chronic illnesses, pain, and personality traits. Medians (interquartile range) are given for education level, medical consumption IRS, BAI, and IDS as these values are not normally distributed. Percentages are given for categorical variables. *P* is derived by analysis of variance (ANOVA) for quantitative, normally distributed variables, Mann Whitney U-test for continuous, non-normally distributed variables, or χ^2 statistics for categorical variables. Significance is inferred at P<0.10.

Table 2 shows the effect of putative correlates of BZD use as opposed to non-use among all subjects. Univariate P values of these analyses are shown in Table 1 which comprises group comparisons conducted with ANOVAs. An ANOVA results in exactly the same P value as a regression analysis.

In multivariate analyses, the following variables were significant correlates of BZD use: older age (OR=1.48), singleness (OR=1.34), unemployment (OR=1.56), treatment in secondary care (OR=1.55), higher medical consumption (OR=1.41), a diagnosis of depression (OR=1.56), anxiety (OR=1.95) and comorbidity (OR=1.78), higher scores on the IRS (OR=1.35) and BAI (OR=1.65) questionnaires, use of SSRIs (OR=2.05), TCAs (OR=1.84), and other antidepressants (OR=2.44).

In the comparison between anxiolytic and hypnotic users, groups were similar on most variables, except of the following: Anxiolytic users were younger (45.3 vs. 47.8, P=0.04), had more often a diagnosis of anxiety (25.2 vs. 14.9%, P=0.02), less often a diagnosis of depression (15.9 vs. 28.9%, P=0.009), had lower scores on insomnia (9.0 vs. 13.0, P≤0.001), and higher scores on agreeableness (31.8 vs. 30.5, P=0.02, data not shown).

Appropriateness of BZD Use

In Table 3, we present the characteristics of BZD use among the 429 BZD users. The median daily dosage used was 2.5 mg of diazepam equivalents (interquartile range [IQR]: 0.7 – 6.0) and the median duration of BZD use was 24 months (IQR: 5.0 – 84.0). The most frequently used BZD was oxazepam (44.3%), followed by temazepam (14.9%), diazepam (14.7%) and alprazolam (6.1%).

Only 17.5% of all BZD users took BZDs for the appropriate duration of three months whereas 82.5% of users took BZDs for a much longer period. The remaining appropriateness criteria were met more frequently. The majority of the BZD users (86.0%) did not exceed the recommended DDD as defined by the WHO and 84.4% of users had only

TABLE 2. Determinants of Benzodiazepine Use as opposed to Non-Use: Results from Univariate and Multivariate logistic Regression Analyses (n=2852)

	Univariate analysis odds ratio (95% CI)	P-value*	Multivariate analysis odds ratio (95% CI)	P value**
Sociodemographics				
Sex (female)	1.09 (0.88 – 1.36)	0.43	1.09 (0.84 – 1.42)	0.53
Age (per 10 years)	1.34 (1.22 – 1.48)	<0.001	1.48 (1.34 – 1.63)	<0.001
Partner status (single)	1.36 (1.10 – 1.69)	0.005	1.34 (1.05 – 1.71)	0.02
Employment status (not working)	2.71 (2.20 – 3.33)	<0.001	1.56 (1.22 – 1.99)	<0.001
Education level (years)	0.30 (0.20 – 0.43)	<0.001	0.89 (0.56 – 1.43)	0.64
Health care setting (secondary care)	3.00 (2.43 – 3.71)	<0.001	1.55 (1.16 – 2.07)	0.003
Physical health				
Medical consumption	2.39 (2.04 – 2.79)	<0.001	1.41 (1.17 – 1.69)	<0.001
Chronic illnesses	1.28 (1.20 – 1.35)	<0.001	1.02 (0.95 – 1.11)	0.54
Pain	1.63 (1.49 – 1.79)	<0.001	1.09 (0.97 – 1.23)	0.13
Smoking	0.79 (0.62 – 1.00)	0.05	0.96 (0.73 – 1.26)	0.77
Psychological Characteristics				
Current Diagnosis				
MDD Only	1.19 (0.91 – 1.56)	0.21	1.56 (1.02 – 2.40)	0.04
Anxiety Only	1.30 (1.00 – 1.71)	0.06	1.95 (1.29 – 2.93)	0.001
Comorbid disorder	3.20 (2.59 – 3.95)	<0.001	1.78 (1.17 – 2.70)	0.008
IRS	2.13 (1.85 – 2.45)	<0.001	1.35 (1.16 – 1.56)	0.001
BAI	2.72 (2.37 – 3.13)	<0.001	1.65 (1.34 – 2.03)	<0.001
IDS-SR Mood/Cognition Scale	2.29 (2.00 – 2.62)	<0.001	0.90 (0.72 – 1.13)	0.36
Antidepressant use (past month)				
SSRI	3.27 (2.60 – 4.12)	<0.001	2.05 (1.55 – 2.70)	<0.001
TCA	3.06 (1.88 – 4.98)	<0.001	1.84 (1.07– 3.16)	0.03
Others	3.74 (2.67 – 5.24)	<0.001	2.44 (1.64 – 3.62)	<0.001
Personality Characteristics				
Neuroticism	1.07 (1.06 – 1.08)	<0.001	0.99 (0.97 – 1.02)	0.61
Extraversion	0.93 (0.92 – 0.95)	<0.001	1.00 (0.98 – 1.02)	0.78
Openness	0.97 (0.95 – 0.99)	<0.001	0.99 (0.97 – 1.01)	0.29
Agreeableness	0.98 (0.96 – 1.00)	0.02	1.01 (0.99 – 1.04)	0.26
Conscientiousness	0.96 (0.94 – 0.97)	<0.001	1.00 (0.98 – 1.02)	0.92

BAI indicates Beck's anxiety index; IDS indicates Inventory of Depressive Symptomatology; IRS indicates Insomnis Rating Scale; MDD indicates Major Depressive Disorder; SSRI indicates Selective Serotonin Reuptake Inhibitor; TCA indicates Tricyclic Antidepressant. All variables with P<0.10 in univariate analyses are entered in the multivariate model. Significance is inferred at P < 0.05 in the multivariate model.*: The P values are optained by univariate analyses. ** : The P values are obtained by multivariate analyses.

TABLE 3. Characteristics and Appropriateness of Benzodiazepine (BZD) Use (n=429)

Benzodiazepine Use	
Type of BZD	
Short acting (%, $t_{1/2}$ < 24h)	81.1
Long acting (%, $t_{1/2}$ ≥ 24h)	18.9
Mean daily dose (mg / day)[1]	2.5 (0.7 – 6.0)
Duration of use (months)	24.0 (5.0 – 84.0)
Daily BZD use (%)	38.5
Number of different types of BZDs used concomitantly (%)	
1	84.4
2	14.0
3	1.6
Most frequently used BZDs (%)	
Oxazepam	44.3
Temazepam	14.9
Diazepam	14.7
Alprazolam	6.1
Lorazepam	4.2
Zopiclone	3.7
Appropriate BZD use	
Mean Daily Dose/ DDD[2] ≤ 1(%)	86.0
Duration of use ≤ 3 months (%)	17.5
Use of only 1 type of BZD (%)	84.4
Inappropriateness score[3] (%)	
0	15.2
1	64.3
2	13.8
3	6.8

[1]Expressed as diazepam equivalents, [2] DDD indicates defined daily dose (DDD for diazepam: 10 mg / day), [3] an appropriateness score of 0 indicates that all appropriateness criteria are met (appropriate use), an appropriateness score of 3 indicates that none of the criteria is met (inappropriate use)

Median (interquartile range) is given for mean daily dose and duration of use. Percentages are given for categorical variables.

TABLE 4. Determinants of Inappropriate[1] Benzodiazepine (BZD) Use: Results from Univariate and Multivariate Linear Regression Analyses (n=429)

	Univariate Analysis β	**P value**	**Multivariate Analysis** β	**P value**
Sociodemographics				
Sex (female)	-0.003	0.96	0.018	0.72
Age (years)	0.153	0.001	0.130	0.008
Partner status (single)	0.065	0.18		
Employment status (not working)	0.114	0.02	0.073	0.14
Education level (years)	-0.078	0.11		
Health care setting (secondary care)	0.010	0.84		
Physical health				
Medical consumption	-0.043	0.37		
Chronic illnesses	0.173	<0.001	0.120	0.02
Pain	0.078	0.11		
Smoking	-0.034	0.48		
Psychological Characteristics				
Current Diagnosis (%)				
MDD Only	-0.067	0.16		
Anxiety Only	-0.028	0.56		
Comorbid disorder	0.060	0.21		
IRS	0.013	0.79		
BAI	0.075	0.12		
IDS-SR Mood/Cognition Scale	0.076	0.12		
Personality Characteristics				
Neuroticism	0.008	0.87		
Extraversion	-0.113	0.02	-0.043	0.40
Openness	-0.098	0.04	-0.065	0.18
Agreeableness	-0.126	0.009	-0.111	0.03
Conscientiousness	-0.017	0.73		

BAI indicates Beck's anxiety index; IDS-SR indicates Inventory of Depressive Symptomatology Self Report; IRS indicates Insomnia Rating Scale; MDD indicates Major Depressive Disorder; SSRI indicates Selective Serotonin Reuptake Inhibitor; TCA indicates Tricyclic Antidepressant.[1] Inappropriate BZD use is calculated with an inappropriateness score. An inappropriateness score of 0 indicates that all appropriateness criteria are met, an inappropriateness score of 3 indicates that none of the criteria is met. All variables with $P < 0.10$ are entered in the multivariate model. Significance in the multivariate analysis is inferred at $P < 0.05$.

a prescription for one type of BZD at a time. However, mainly due to the high duration of BZD use of most users, only 15.2% of BZD users met all three appropriateness criteria, whereas 64.3% met two criteria, 13.8% met one and 6.8% of users did not meet any criterion (highly inappropriate use).

Table 4 shows the effect of potential correlates of inappropriate BZD use among all BZD users. Age (β = 0.130) and chronic illnesses (β = 0.120) were significantly associated with higher inappropriate BZD use. Higher scores on agreeableness were associated with lower inappropriate use (β = -0.111).

DISCUSSION

BZDs were used by a considerable proportion of the 2852 NESDA participants (15.0%). BZD use was independently associated with older age, singleness, unemployment, treatment in secondary care, high medical consumption, (more severe) anxiety, depression, comorbidity, (more severe) insomnia, and antidepressant use. Inappropriate BZD use was independently associated with older age and chronic illnesses. High scores on agreeableness were associated with less inappropriate use. Overall, BZD use was rarely in accordance with all guidelines, mainly because most users (82.5%) exceeded the recommended maximum duration for safe use.

Although the uncritical enthusiasm about BZD use is over since many decades,[30,47,48] BZDs are still not only used for the treatment of severe insomnia and anxiety (other than epilepsy), but also to alleviate stress caused by adverse life circumstances such as unemployment[49] as well as pain[6] and other somatic complaints.[1] Largely corresponding to earlier findings, our results show that mainly the physically and mentally more vulnerable, e.g., the old,[5,13,29] unemployed,[12,13,15] psychologically,[3,13,15-17,32-34] and physically[14,18,34] ill subjects are using BZDs and use these BZDs inappropriately. There seems to be a tendency from

relatively invulnerable subjects being non-users, mildly vulnerable being users and highly vulnerable being inappropriate users. Consistently, vulnerable subjects reported lower perceived support[50,51,52] as well as more maladaptive coping strategies[18,32,50-53] and were found to display more emotional arousal when facing stressful events as compared to less vulnerable subjects.[49] They might substitute those deficits by BZDs[49,52] and be more likely to ask their medical doctors (MDs) for tranquillizers to alleviate their distress. MDs themselves might also be more likely to prescribe BZDs to vulnerable subjects as compared with all other problems those people have due to unemployment, chronic illnesses and psychopathology, BZD use seems to be the least concerning issue. A number of qualitative research studies investigated the prescription habits of MDs and found that the majority of questioned MDs were aware of the guidelines[54,55] and supported conservative prescription practice of BZDs.[54] A reported reason for prescribing nonetheless was feeling poorly equipped to solve the emotional problems of their troubled patients,[56] but wanting to alleviate their distress[55] and maintain a good doctor-patient relationship.[54,55] If MDs received more (psychological) education on how to communicate their reasons for declining prescriptions to the patients, they might prescribe less and initiate BZD discontinuation more often.[54,56,57]

As could be expected, anxiolytic BZDs were more often used in cases of anxiety disorders, and hypnotic BZDs more often in cases of insomnia. However, it also seems that the drugs are insufficient to provide therapeutic relief as otherwise lower anxiety and insomnia scores were to be expected in the respective groups. Group differences on age and agreeableness were unexpected and difficult to explain.

In general, the high percentage of inappropriate users in NESDA is disconcerting. The majority (84.8%) of users did not use BZDs according to international guidelines,[25-27] mainly due to exceeding the maximum duration of recommended use. This is striking considering that for more than 20 years BZDs have been known to cause side effects and

dependence and evidence for the drug's effectiveness in long-term use is controversial.[7,8] In addition, several NESDA subjects surpassed the recommended daily dosage (14.0%) and used more than one type of BZD concomitantly (15.6%). Dosage escalation is generally unsafe, as side effects become more pronounced and can have adverse consequences ranging from low performance at work to falls and traffic accidents.[6,20-22] BZDs should be reserved for the severely anxious who have tried AD medication with no effect and have BZDs as last treatment option. However, BZD prescriptions cannot be discontinued without providing patients with alternative coping strategies. Training should be conducted to strengthen BZD users' coping skills,[11,58] self-efficacy and positive outcome expectations[11] and to lessen their disengagement beliefs[11] as such efforts may increase the chance of successful BZD discontinuation.[11,58] In spite of all objections and in view of the restricted financial resources in the health sector, it is clear that prescribing BZDs takes less time than providing psychological support.[7,55] Therefore, BZD use should be targeted with relatively quick and cheap methods that have been developed (e.g., computer-tailored education,[11] discontinuation letters[59]) and found to increase effectively BZD cessation rates.[11,59]

The present study has some limitations. The cross-sectional design does not allow us to make causal inferences on whether determinants preceded BZD use or vice versa. Although participants were asked to bring drug containers to the interview, one fourth of the subjects did not adhere to that and reported medication use from memory leading to a potential recall bias. The 84.8% inappropriate user number is probably an overestimation, as long-term users were more likely to be included in the user group than short-term users due to the cross-sectional design. A strong aspect of our study is the conductance of a multivariate analysis across a comprehensive set of possible determinants of BZD use. Furthermore, we included all aspects of inappropriate BZD use in a large sample composed of subjects with a range of psychopathology.

In conclusion, this study revealed three major points: 1) the vast majority of NESDA subjects displayed inappropriate BZD use, mainly due to exceeding the maximum duration of recommended use; 2) it is primarily the physically or mentally vulnerable subjects who use BZDs, and 3) the most physically ill of the BZD users are at highest risk for inappropriate use. Without further evidence for the effectiveness of BZDs in long-term use, caution in initiating BZD prescriptions is recommended, particularly when patients are chronically ill and old, as these subjects are most likely to display inappropriate use.

REFERENCES

1. van Hulten R, Heerdink ER, Bakker A, et al. Benzodiazepine pathways in the chronically ill. *Pharmacoepidemiology and Drug Safety*. 1999;8:325-330.
2. Barker MJ, Greenwood KM, Jackson M, et al. Persistence of cognitive effects after withdrawal from long-term benzodiazepine use: a meta-analysis. *Arch Clin Neuropsychol*. 2004;19:437-454.
3. Morin CM, Belanger L, Bernier F. Correlates of benzodiazepine use in individuals with insomnia. *Sleep Medicine*. 2004;5:457-462.
4. Nolan L, Omalley K. Patients, Prescribing, and Benzodiazepines. *European Journal of Clinical Pharmacology*. 1988;35:225-229.
5. van Hulten R, Leufkens HG, Bakker A. Usage patterns of benzodiazepines in a Dutch community: a 10-year follow-up. *Pharm World Sci*. 1998;20:78-82.
6. Neutel CI. The epidemiology of long-term benzodiazepine use. *International Review of Psychiatry*. 2005;17:189-197.
7. Lader M. Benzodiazepines - Opium of Masses. *Neuroscience*. 1978;3:159-165.
8. Weil A, Rosen W. From Chocolate to Morphine: Everything You Need to Know About Mind-Altering Drugs (Paperback). 1998.
9. Ribeiro CS, Azevedo RCS, da Silva VF, et al. Chronic use of diazepam in primary healthcare centers: user profile and usage pattern. *Sao Paulo Medical Journal*. 2007;125:270-274.
10. Barbui C, Gregis M, Zappa M. A cross-sectional audit of benzodiazepine use among general practice patients. *Acta Psychiatr Scand*. 1998;97:153-156.
11. Ten Wolde GB, Dijkstra A, Van Empelen P, et al. Social-cognitive predictors of intended and actual benzodiazepine cessation among chronic benzodiazepine users. *Addictive Behaviors*. 2008;33:1091-1103.
12. Magrini N, Vaccheri A, Parma E, et al. Use of benzodiazepines in the Italian general population: prevalence, pattern of use and risk factors for use. *Eur J Clin Pharmacol*. 1996;50:19-25.
13. Olfson M, Pincus HA. Use of Benzodiazepines in the Community. *Archives of Internal Medicine*. 1994;154:1235-1240.

14. Lagro-Janssen AL, Liberton IJ. [Profiles of regular consumers of benzodiazepines in a family practice]. *Ned Tijdschr Geneeskd*. 1993;137:1969-1973.
15. Ashton H, Golding JF. Tranquillisers: prevalence, predictors and possible consequences. Data from a large United Kingdom survey. *Br J Addict*. 1989;84:541-546.
16. Mant A, Mattick RP, Deburgh S, et al. Benzodiazepine Prescribing in General-Practice - Dispelling Some Myths. *Family Practice*. 1995;12:37-43.
17. Salinsky JV, Dore CJ. Characteristics of long term benzodiazepine users in general practice. *J R Coll Gen Pract*. 1987;37:202-204.
18. Simpson RJ, Power KG, Wallace LA, et al. Controlled Comparison of the Characteristics of Long-Term Benzodiazepine Users in General-Practice. *British Journal of General Practice*. 1990;40:22-26.
19. Salzman C. The APA Task Force report on benzodiazepine dependence, toxicity, and abuse. *Am J Psychiatry*. 1991;148:151-152.
20. Paterniti S, Dufouil C, Alperovitch A. Long-term benzodiazepine use and cognitive decline in the elderly: the Epidemiology of Vascular Aging Study. *J Clin Psychopharmacol*. 2002;22:285-293.
21. Thomas RE. Benzodiazepine use and motor vehicle accidents - Systematic review of reported association. *Canadian Family Physician*. 1998;44:799.
22. Kan CC, Breteler MHM, Zitman FG. High prevalence of benzodiazepine dependence in out-patient users, based on the DSM-III-R and ICD-10 criteria. *Acta Psychiatrica Scandinavica*. 1997;96:85-93.
23. Rapoport MJ, Lanctot KL, Streiner DL, et al. Benzodiazepine Use and Driving: A Meta-Analysis. *Journal of Clinical Psychiatry*. 2009;70:663-673.
24. Comittee on the review of medicines. Systematic Review of the Benzodiazepines: Guidelines for data sheets on diazepam, chlordiazepoxide, medazepam, clorazepate, lorazepam, oxazepam, temazepam, triazolam, nitrazepam, and flurazepam. *British Medical Journal*. 1980;280:910-912.
25. National Collaborating Center for Primary Care. Management of anxiety (panic disorder, with or without agoraphobia, and generalized anxiety disorder) in adults in primary, secondary, and community care. *NICE clinical guideline 22*. 2007.

26. Knuistingh Neven A, Lucassen P, Bonsema K, et al. Practice guideline for insomnia and hypnotics (Dutch College of Genera; Practitioners). [In Dutch: NHG-Standaard Slapeloosheid en slaapmiddelen]. *Huisarts & Wetenschap*. 2005;48:402-415.
27. Terluin B, van Heest F, van der Meer K, et al. NHG-Standaard Angststoornissen (eerste herziening). *Huisarts Wet*. 2004;47:26-37.
28. Isacson D. Long-term benzodiazepine use: factors of importance and the development of individual use patterns over time--a 13-year follow-up in a Swedish community. *Soc Sci Med*. 1997;44:1871-1880.
29. Isacson D, Carsjo K, Bergman U, et al. Long-Term Use of Benzodiazepines in A Swedish Community - An 8-Year Follow-Up. *Journal of Clinical Epidemiology*. 1992;45:429-436.
30. Mellinger GD, Balter MB, Uhlenhuth EH. Prevalence and correlates of the long-term regular use of anxiolytics. *JAMA*. 1984;251:375-379.
31. Simon GE, VonKorff M, Barlow W, et al. Predictors of chronic benzodiazepine use in a health maintenance organization sample. *Journal of Clinical Epidemiology*. 1996;49:1067-1073.
32. Zandstra SM, van Rijswijk E, Rijnders CAT, et al. Long-term benzodiazepine users in family practice: differences from short-term users in mental health, coping behaviour and psychological characteristics. *Family Practice*. 2004;21:266-269.
33. Zandstra SM, Furer JW, van de Lisdonk EH, et al. Differences in health status between long-term and short-term benzodiazepine users. *British Journal of General Practice*. 2002;52:805-808.
34. Luijendijk HJ, Tiemeier H, Hofman A, et al. Determinants of chronic benzodiazepine use in the elderly: a longitudinal study. *Br J Clin Pharmacol*. 2008;65:593-599.
35. Penninx BWJH, Beekman ATF, Smit JH, et al. The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and methods. *International Journal of Methods in Psychiatric Research*. 2008;17:121-140.
36. Riss J, Cloyd J, Gates J, et al. Benzodiazepines in epilepsy: pharmacology and pharmacokinetics. *Acta Neurologica Scandinavica*. 2008;118:69-86.
37. WHO Collaborating Centre for Drug Statistics Methodology (2010). ATC/DDD System. In WHO Collaborating Centre for Drug Statistics

Methodology. Available via http://www.whocc.no/atc_ddd_index. Accessed 22 march 2010.

38. Manthey L, Giltay EJ, Van Veen T, et al. Long-Term Benzodiazepine Use and Salivary Cortisol The Netherlands Study of Depression and Anxiety (NESDA). *Journal of Clinical Psychopharmacology*. 2010;30:160-168.
39. Zitman FGr. Discontinueringsstrategieen. *In: Kahn RS, Zitman FG, redacteuren Farmacotherapie in de psychiatrie*. 1999;165-177.
40. Wells KB, Kamberg C, Brook R, et al. Health status, sociodemographic factors, and the use of prescribed psychotropic drugs. *Med Care*. 1985;23:1295-1306.
41. Beck AT, Epstein N, Brown G, et al. An inventory for measuring clinical anxiety: psychometric properties. *J Consult Clin Psychol*. 1988;56:893-897.
42. Levine DW, Kripke DF, Kaplan RA, et al. Reliability and validity of the Women's Health Initiative Insomnia Rating Scale. *Psychological Assessment*. 2003;15:137-148.
43. Wardenaar KJ, Van Veen T, Giltay EJ, et al. The structure and dimensionality of the Inventory of Depressive Symptomatology Self Report (IDS-SR) in patients with depressive disorders and healthy controls. *J Affect Disord*. 2010; 125(1-3) :146-54.
44. Costa PT, McCrae RR. Domains and facets: hierarchical personality assessment using the revised NEO personality inventory. *Journal of Personality Assessment*. 1995;64:21-50.
45. Meadows GN, Burgess PM. Perceived need for mental health care: findings from the 2007 Australian Survey of Mental Health and Wellbeing. *Australian and New Zealand Journal of Psychiatry*. 2009;43:624-634.
46. VonKorff M, Ormel J, Keefe FJ, et al. Grading the Severity of Chronic Pain. *Pain*. 1992;50:133-149.
47. Ladewig D. Dependence Liability of the Benzodiazepines. *Drug and Alcohol Dependence*. 1984;13:139-149.
48. Laux G, Konig W. Benzodiazepines - Long-Term Use Or Abuse - Results of An Epidemiological-Study. *Deutsche Medizinische Wochenschrift*. 1985;110:1285-1290.
49. Perodeau G, Cappeliez P. Quality of life and benzodiazepine drug use by community-dwelling elderly: a stress and coping perspective. *European*

Review of Applied Psychology-Revue Europeenne de Psychologie Appliquee. 2007;57:193-200.

50. Coyne JC, Downey G. Social-Factors and Psychopathology - Stress, Social Support, and Coping Processes. *Annual Review of Psychology*. 1991;42:401-425.
51. Kessler RC, Price RH, Wortman CB. Social-Factors in Psychopathology - Stress, Social Support, and Coping Processes. *Annual Review of Psychology*. 1985;36:531-572.
52. Parr JM, Kavanagh DJ, Young RM, et al. Views of general practitioners and benzodiazepine users on benzodiazepines: A qualitative analysis. *Social Science & Medicine*. 2006;62:1237-1249.
53. Greenwald DF, Harder DW. Fantasies, coping behavior, and psychopathology (Reprinted from Journal of Clinical Psychology, vol 53, pg 91-97, 1997). *Journal of Clinical Psychology*. 2003;59:1089-1095.
54. Bendtsen P, Hensing G, McKenzie L, et al. Prescribing benzodiazepines - a critical incident study of a physician dilemma. *Social Science & Medicine*. 1999;49:459-467.
55. Cook JM, Marshall R, Masci C, et al. Physicians' perspectives on prescribing benzodiazepines for older adults: A qualitative study. *Journal of General Internal Medicine*. 2007;22:303-307.
56. Cormack MA, Howells E. Factors Linked to the Prescribing of Benzodiazepines by General-Practice Principals and Trainees. *Family Practice*. 1992;9:466-471.
57. Boixet M, Batlle E, Bolibar I. Benzodiazepines in primary health care: A survey of general practitioners prescribing patterns. *Addiction*. 1996;91:549-556.
58. Bish A, Golombok S, Hallstrom C, et al. The role of coping strategies in protecting individuals against long-term tranquillizer use. *British Journal of Medical Psychology*. 1996;69:101-115.
59. Gorgels WJMJ, Voshaar RCO, Mol AJJ, et al. Discontinuation of long-term benzodiazepine use by sending a letter to users in family practice: a prospective controlled intervention study. *Drug and Alcohol Dependence*. 2005;78:49-56.