Universiteit
Leiden
The Netherlands

Determinants and consequences of long-term benzodiazepine use

Manthey, L.

Citation
Manthey, L. (2012, December 6). *Determinants and consequences of long-term benzodiazepine use*. Retrieved from https://hdl.handle.net/1887/20252

Version:	Corrected Publisher's Version
License:	Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden
Downloaded from:	https://hdl.handle.net/1887/20252

Note: To cite this publication please use the final published version (if applicable).

Cover Page

Universiteit Leiden

The handle http://hdl.handle.net/1887/20252 holds various files of this Leiden University dissertation.

Author: Manthey, Leonie
Title: Determinants and consequences of long-term benzodiazepine use
Date: 2012-12-06

Determinants of Initiated and Continued Benzodiazepine Use in the Netherlands Study of Depression and Anxiety (NESDA)

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

3

Journal of Clinical Psychopharmacology
2011, 31 (6): 774 - 779

ABSTRACT

Background: Longitudinal research on determinants of initiated and continued benzodiazepine (BZD) use is inconsistent and has identified many possible determinants. It is unclear which of those are most important in the prediction of BZD use. We aimed to identify the most important predictors of initiated and continued BZD use. Therefore, we analyzed the most consistently identified determinants from previous research plus some new determinants.

Method: We identified baseline and 2-year longitudinal predictors of initiated BZD use (vs nonuse) among 2205 baseline BZD nonusers, and of continued use (vs discontinued use) among 369 baseline BZD users in the Netherlands Study of Depression and Anxiety using logistic regression analyses.

Results: During follow-up, BZD use was initiated by 4.9% of BZD nonusers at baseline. Initiated use was predicted by insomnia (odds ratio [OR]=1.60), enduring anxiety symptoms (OR=2.02), entering secondary care during follow-up (OR=2.85), and past BZD use (OR=3.57). Positive life events during follow-up reduced the likelihood of BZD initiation (OR=0.76). Of BZD users at baseline, 54.2% continued use during the entire follow-up period. Continuation of BZD use was predicted by higher age (OR=1.03), severe anxiety (OR=1.85), and a long duration of BZD use (OR=1.54). Leaving secondary care was associated with less continued BZD use (OR=0.29).

Conclusion: Insomnia and anxiety were the main risk factors of initiated use, whereas advanced age and anxiety severity were the main risk factors of continued use. Gender, education, pain, and physical health seemed to be less important.

INTRODUCTION

Benzodiazepines (BZDs) are an effective short-term treatment option for symptoms of anxiety and insomnia.[1-3] Although BZDs are often the indicated treatment,[4] they are also inappropriately used for psychosocial problems,[5] pain,[6] and somatic complaints.[3,7] As BZDs are associated with dose- and concentration related side effects and physiological dependence,[1,3,8] guidelines advise short-term use.[4,9,10] Still, many BZD users are long-term users.[6] The existence of chronic and inappropriate BZD prescriptions call for the identification of risk factors of initiation and continuation of BZD use.

Cross-sectional research has identified many correlates of BZD use, but could not establish the temporal order of events.[11] Longitudinal analyses permit to establish the order of events and to identify true risk factors of BZD use. In longitudinal studies, initiated BZD use was predicted by female gender,[12] older age,[12] divorce,[12] psychopathology,[13] insomnia,[14] alcohol abuse,[13] antidepressant use,[13] smoking,[14] poor physical health,[14] and joint pain.[14] Continued BZD use was predicted by older age,[14] female gender,[15] divorce,[15] psychopathology,[16] poor health,[17] pain,[14] number of GP contacts,[15] insomnia,[15] a history of BZD use,[17] daily BZD use,[18] use of higher potency BZDs,[19] long duration of BZD use,[20] high BZD dosage,[20] and hypnotic use.[20] Living alone was associated with a decreased risk of continued BZD use.[14] However, findings are inconsistent across studies, possibly due to the investigation of only a few determinants per study,[12] distinct definitions of the outcome variable (psychotropic use,[12] BZD use,[18] onset of use,[16] onset of chronic use[14]), dissimilar data collection (pharmacy databases,[18] self-report [21]), differing study samples (all ages,[22] old subjects [5]) and included determinants. Thus, it remains unclear which of the above mentioned predictors are most important in the prediction of BZD use. Additionally, the associations of course of psychopathology and life events with BZD use have not been studied in longitudinal research yet.

We aimed to identify the (most important) independent risk factors of initiated BZD use and continued BZD use during a 2-year follow-up period. Therefore, we included the above described previously investigated predictors of BZD use and several not previously investigated determinants (e.g., course of psychopathology and life events) in order to investigate which variables would fall off (and thus be less relevant) and which would remain significant in the a multivariate model.

MATERIALS AND METHODS

Subjects

Subjects participated in the baseline and 2-year assessment of the Netherlands Study of Depression and Anxiety (NESDA), an ongoing 8-year longitudinal cohort study of 2981 respondents aged 18 through 65 years.[23] NESDA was designed to be representative of individuals with depressive and/or anxiety disorders in different health care settings and developmental stages of illness. Therefore, subjects with no symptoms ("controls"), those with earlier episodes or at risk, and those with a depressive or anxiety disorder were recruited from the community, general practices and specialized mental health care institutions throughout the Netherlands.[23] The baseline assessment included a medical exam, an in-person interview, and self-report questionnaires.[23] The study protocol was approved by the Ethical Review Board of each participating center and all subjects signed an informed consent at the baseline assessment.[23] After 2 years, a face-to-face follow-up was conducted.[24] Data from baseline and follow-up were used in this analysis. We excluded subjects with lacking follow-up data (n=385) and those with epilepsy (n=22), as epilepsy can be an indication for long-term BZD use.[25] Missing data were imputed by the mean for 4.2 % of data points. Imputation did not importantly change our results. After exclusion, 2574 subjects remained and comprised the sample of the following analyses.

To identify the determinants of initiated BZD use, only subjects who did not use BZDs at baseline were included (n=2205). They were divided into subjects who initiated BZD use in the time interval between baseline and follow-up ("initiated use", n=103) and those who did not ("nonuse", n=2102). For the investigation of continued BZD use, only subjects who used BZDs at baseline were included (n=369) and divided into subjects who still reported BZD use at follow-up ("continued use", n=200) and subjects who had discontinued use between baseline and follow-up ("discontinued use", n=169).

MEASURES

BZD Use

BZD use at baseline/follow-up (including z-drugs; Anatomical Therapeutic Codes [ATC codes] N05BA, N05CD, N03AE01 and N05CF[26]) was defined as having used BZDs (daily or less often) in the month before the baseline/follow-up interview. It was registered by observation of drug containers brought to the interview (in 74.3% of cases) or self-report. Information was collected about name, dose, number of tablets, frequency and duration of BZD use.[11]

Possible Determinants of Initiated and Continued BZD Use

To extract a set of the most important determinants of initiated and continued BZD use, the following variables were selected:

1) baseline characteristics (sociodemographic, physical, and psychological characteristics),
2) characteristics of BZD use (daily use, dosage, duration, half-life, number of different BZDs, and dependence), and
3) longitudinal characteristics (duration of psychopathology symptoms during follow-up, life events during follow-up, changes in treatment setting, insomnia, and chronic illnesses).

Baseline characteristics and characteristics of BZD use had been investigated in the past whereas no previous research has studied the above mentioned longitudinal characteristics of BZD use.

Baseline Characteristics

Sociodemographic characteristics. Gender, age, education level (in years), work status (employed, retired/working in household, unemployed/sick leave/disabled), partner status (partner, single, widowed/divorced), and living status (living together with at least 1 person versus living alone) were reported in the baseline interview.

Psychological characteristics. Six-months depressive and anxiety disorders were measured by the Composite International Diagnostic Interview (life time version 2.1) at baseline, which classifies diagnoses according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria. Severity of anxiety symptoms was assessed with the Beck Anxiety Inventory.[27] The presence of insomnia was determined using the Insomnia Rating Scale.[28] The severity of depressive symptoms was measured by the cognitive/mood scale of the Inventory of Depressive Symptomatology Self Report.[29] Locus of control was assessed by a 5-item mastery scale.[30] Personality traits were assessed with the Neuroticism Extraversion Openness-Five Factor Inventory.[31] Antidepressant use (with ATC codes N06AA, N06AB, N06AF, N06AX or N06AG) was reported during the interview.

Physical characteristics. An inventory of somatic diseases was made by counting the number of chronic illnesses a subject experienced at the baseline assessment.[11] The number of GP consultations in the 6 months before baseline assessment was assessed with the trimbos/iMTA questionnaire for costs associated with psychiatric illness.[32] Pain complaints were measured with the Chronic Graded Pain Scale.[33] Smoking was reported during the interview. Alcohol dependence was assessed with the corresponding Composite International Diagnostic Interview section.[34]

Characteristics of BZD Use at Baseline

As characteristics of use were associated with continued use in previous research,[18,19] mean daily dose, frequency of use, half-life, number of different types of BZDs used, and BZD dependency were included as possible predictors of continued BZD use.[11]

Longitudinal Characteristics (Measured During the 2-year Follow-Up)

Duration of psychopathology symptoms. The percentage of time during follow-up with symptoms of at least mild severity was calculated using the Life Chart Interview.[35] Three categories were established: 1) no anxiety/depressive symptoms during follow-up, 2) less than half of follow-up anxiety/depressive symptoms, and 3) more than half of follow-up anxiety/depressive symptoms.

Life events. The incidence of 12 negative life events during follow-up was assessed with the List of Threatening Events Questionnaire.[36] The List of Threatening Events Questionnaire was extended by 7 items referring to positive life events: (1) "immediate family member recovered from serious illness", (2) "met a new partner", (3) "became friends", (4) "have been on holiday", (5) "new job or important promotion", (6) "education completed", and (7) "be better off financially". Numbers of negative and positive life events during the follow-up period were summed separately in order to derive separate measures for the number of negative and positive life events.

Other longitudinal measures. Severity of insomnia and number of chronic illnesses at follow-up were assessed using similar methods as at baseline. For insomnia severity and chronic illnesses a change score was calculated by subtracting the baseline value from the follow-up value. A higher score indicated worsening of illnesses/insomnia from baseline to follow-up and vice versa. Treatment setting (primary vs secondary care) was established at baseline and follow-up. Transitions in treatment setting were divided in 4 categories: 1) primary care only, 2) entry of

secondary care during follow-up, 3) exit of secondary care during follow-up, and 4) secondary care only.

STATISTICAL ANALYSES

Sample characteristics were expressed by frequencies or means and compared using $\chi 2$ statistics and analysis of variance (ANOVA). Univariate logistic regression analyses were carried out to identify predictors of initiated BZD use (vs nonuse [reference]) among baseline BZD nonusers and continued use (vs discontinued use [reference]) among baseline BZD users. Variables with $P < 0.10$ in univariate analyses were entered in the multivariate regression models. In these analyses, baseline characteristics, longitudinal characteristics and characteristics of BZD use (only for analysis of continued use, except of history of BZD use which was only entered in the analysis of initiated use) were considered. All analyses were adjusted for gender and age. Analyses were conducted with SPSS 16.0 for Windows. Significance was inferred at $P < 0.05$.

RESULTS

BZD Use

The prevalence rates of BZD use at baseline and follow-up were 14.3% and 11.8%, respectively. During follow-up, 4.9% of nonusers initiated BZD use. Of the BZD (n=369) users at baseline, 54.2% continued use during the entire follow-up period. At baseline, there were 135 daily BZD users and 234 infrequent users, of whom 49.1% used BZDs as needed. At follow-up, there were 89 daily users and 214 infrequent users, of whom 59.3% used as needed. Short-acting BZDs were most often used, with on average 20.7% using long-acting BZDs at baseline and follow-up.

Predictors of Initiated BZD Use

Table 1 shows the baseline and longitudinal characteristics of baseline nonusers who initiated BZD use in the follow-up period (4.6%) or remained nonusers. In multivariate analyses, higher baseline insomnia (OR=1.60), anxiety symptoms for more than half of the follow-up time (OR=2.02), entering secondary care during follow-up (OR=2.85), and past BZD use (OR=3.57) were independent predictors of initiated BZD use. A higher number of positive life events experienced during follow-up decreased the probability of BZD use initiation (OR per positive life event=0.76).

Predictors of Continued BZD Use

In Table 2, we present the characteristics of subjects who continued BZD use (n=200) as compared with those who discontinued BZD use (n=169) as investigated in subjects who were using BZDs at baseline (n=369). In multivariate analyses, older age (OR per year=1.03), higher anxiety severity (OR per Beck Anxiety Inventory point=1.85), and a longer duration of BZD use at baseline (OR per month=1.54) predicted the continuation of BZD use. Leaving secondary care treatment during the follow-up time was associated with a lower OR of continued BZD use (OR=0.29).

TABLE 1. Baseline and Longitudinal Characteristics of Nonusers (at Baseline) Who Initiated Versus Did Not Initiate BZD Use (n=2205)

	No Initiated Use n= 2102	**Initiated Use n=103**	***P****	**Multivariate OR for Initiated Use**	***P*** **
Baseline characteristics					
Sociodemographics					
Sex (% female)	65.9	64.1	0.71	0.81 (0.51-1.27)	0.35
Age (years)	41.2 (40.6-41.7)	44.3 (41.8-46.9)	0.02	1.01 (0.99-1.03)	0.50
Partner status (%)					
Current partner	70.6	62.1	0.12		
No current partner	21.3	25.2			
Widowed / divorced	8.0	12.6			
Living status (% alone)	27.2	33.0	0.20		
Employment status (%)			0.005		
Employed	64.6	49.5			
Pension/housewife	3.6	6.8		2.25 (0.88-5.78)	0.09
Unemployed / sick	31.8	43.7		1.23 (0.78-1.96)	0.38
Education level (years)	14.1 (14.0-14.2)	13.3 (12.8-14.0)	0.02	0.73 (0.29-1.84)	0.51
Physical health					
Medical consumption	3.9 (3.8-3.9)	4.3 (4.0-4.7)	0.02	0.85 (0.54-1.33)	0.47
Chronic illnesses	3.5 (3.4-3.6)	3.9 (3.6-4.2)	0.005	1.12 (0.60-2.06)	0.73
Pain	3.4 (3.3-3.4)	3.8 (3.6-4.0)	<0.001	1.79 (0.75-4.29)	0.19
Smoking (%)	29.6	28.2	0.75		
Alcohol dependence (%)	26.2	32.0	0.19		
Psychological Characteristics					
Six months diagnosis (%)			<0.001		
No diagnosis	53.3	27.2			
MDD only	14.1	12.6		0.81 (0.36-1.84)	0.61
Anxiety only	15.0	26.2		1.56 (0.79-3.09)	0.20
Comorbid disorder	17.6	34.0		1.01 (0.40-2.56)	0.98
Insomnia rating scale	8.3 (8.1-8.5)	11.3 (10.2-12.5)	<0.001	1.60 (1.17-2.18)	**0.003**
Beck Anxiety Inventory	8.8 (8.5-9.1)	14.0 (12.0-16.5)	<0.001	1.07 (0.74-1.54)	0.72
IDS Mood/Cognition Scale	6.5 (6.3-6.8)	9.2 (8.0-10.6)	<0.001	0.87 (0.59-1.29)	0.49
Locus of control	17.9 (17.7-18.0)	16.1 (15.3-16.9)	<0.001	1.16 (0.87-1.55)	0.31
Antidepressant use (%)	17.2	32.0	<0.001	1.43 (0.87-2.37)	0.16
Past BZD use (%)	12.6	44.7	<0.001	3.57 (2.26-5.63)	**<0.001**
Personality Characteristics					
Neuroticism	22.6 (22.2-23.0)	27.1 (25.2-28.9)	<0.001	1.11 (0.79-1.55)	0.56
Extraversion	25.5 (25.2-25.8)	22.7 (21.2-24.3)	<0.001	1.01 (0.76-1.35)	0.92
Openness	26.3 (26.1-26.6)	26.4 (25.1-27.6)	0.98		

Table 1. continued

Agreeableness	31.7 (31.4-31.9)	31.9 (30.7-33.0)	0.78		
Conscientiousness	30.3 (30.0-30.6)	28.8 (27.5-30.1)	0.03	0.97 (0.76-1.24)	0.79
Longitudinal characteristics					
Follow-up time anxiety symptoms (%)			<0.001		
No anxiety symptoms	55.8	29.1			
(Less than) half of time symptoms	18.7	18.4		1.23 (0.64-2.38)	0.53
More than half of time symptoms	25.5	52.4		2.02 (1.14-3.56)	**0.02**
Follow-up time depressive symptoms (%)			0.001		
No depressive symptoms	57.1	37.9			
(Less than) half of time symptoms	4.6	5.8		1.74 (0.66-4.56)	0.26
More than half of time symptoms	38.3	56.3		0.94 (0.55-1.62)	0.83
Life Events					
Number positive life events	2.0 (2.0-2.1)	1.6 (1.3-1.8)	<0.001	0.76 (0.61-0.95)	**0.01**
Number negative life events	2.2 (2.1-2.3)	2.4 (2.1-2.7)	0.15		
Switch of treatment setting (%)			<0.001		
Always primary care	72.8	46.6			
Exit secondary care	7.2	8.7		1.23 (0.53-2.85))	0.64
Entry secondary care	5.0	13.6		2.85 (1.38-5.90)	**0.005**
Always secondary care	15.0	31.1		1.70 (0.92-3.16)	0.09
Change number chronic illnesses	-0.4 (-0.4- -0.3)	-0.5 (-0.7 - -0.3)	0.30		
Change Insomnia Rating scale	-1.4 (-1.6 – 1.2)	-2.4 (-3.3 - -1.5)	0.04	1.02 (0.97-1.07)	0.53

BZD indicates benzodiazepine; IDS indicates Inventory of Depressive Symptomatology; MDD indicates Major Depressive Disorder; OR indicates odds ratio, CI indicates confidence interval. Means (95% confidence intervals) are given for age, personality traits, negative life events, positive life events, change in chronic illnesses, and change in insomnia rating scale. Geometric means (95% CI) based on estimated marginal means and calculated by analysis of variance (ANOVA), are presented for education, medical consumption, chronic illnesses, pain, Insomnia Rating Scale, Beck Anxiety Inventory, and IDS Mood / Cognition Scale as these values are not normally distributed. Percentages are given for categorical variables. *P is derived by ANOVA for quantitative variables or χ^2 statistics for categorical variables. ** P is derived by multivariate logistic regression. All variables with $P < 0.10$ in univariate analyses are entered into the multivariate regression model. The analysis is corrected for sex, age and previous BZD use. Significance is inferred at $P < 0.05$

TABLE 2. Baseline and Longitudinal Characteristics of Users (at Baseline) Who Continued Versus Did Not Continue BZD use (n=369)

	Discontinued Use n= 169	**Continued use n=200**	***P** **	**Multivariate OR (95% CI) for Continued use**	***P** ***
Baseline characteristics					
Sociodemographics					
Sex (% female)	63.3	71.0	0.12	1.28 (0.75-2.18)	0.37
Age (years)	43.2 (41.5-44.9)	49.0 (47.4-50.5)	<0.001	1.03 (1.01-1.06)	**0.02**
Partner status (%)					
Current Partner	66.9	61.0	0.07		
No current partner	23.1	20.5		1.53 (0.81-2.89)	0.19
Widowed/divorced	10.1	18.5		1.76 (0.83-3.69)	0.14
Living status (% alone)	32.0	36.5	0.36		
Employment status (%)			0.03		
Employed	49.1	35.5			
Pension/housewife	4.1	4.5		1.14 (0.33-3.90)	0.83
Unemployed/sick	46.7	60.0		1.45 (0.86-2.45)	0.16
Education level (years)	13.5 (13.0-14.1)	12.5 (12.1-13.0)	0.003	0.62 (0.23-1.67)	0.35
Physical health					
Medical consumption	5.2 (4.8-5.7)	5.5 (5.1-6.0)	0.43		
Chronic illnesses	4.0 (3.7-4.2)	4.3 (4.1-4.6)	0.03	0.70 (0.35-1.39)	0.31
Pain	3.8 (3.7-4.0)	4.0 (3.8-4.1)	0.19		
Smoking (%)	27.8	22.0	0.20		
Alcohol dependence (%)	26.0	28.5	0.60		
Psychological Characteristics					
Six months diagnosis (%)			0.61		
No diagnosis	20.1	18.0			
MDD only	18.9	16.0			
Anxiety only	21.3	19.5			
Comorbid disorder	39.6	46.5			
Insomnia rating scale	11.4 (10.6-12.3)	12.2 (11.4-13.0)	0.21		
Beck Anxiety Inventory	15.2 (13.7-16.8)	19.0 (17.2-20.9)	0.002	1.85 (1.28-2.69)	**0.001**
IDS Mood/Cognition Scale	10.4 (9.4-11.5)	11.5 (10.5-12.6)	0.14		
Locus of control	15.6 (14.9-16.2)	15.0 (14.4-15.6)	0.19		
Antidepressant use (%)	45.0	45.5	0.92		
Personality Characteristics					
Neuroticism	28.0 (26.7-29.2)	28.7 (27.6-29.9)	0.37		
Extraversion	22.1 (21.1-23.2)	21.7 (20.7-22.6)	0.50		
Openness	25.6 (24.6-26.6)	25.0 (24.0-25.9)	0.34		
Agreeableness	31.1 (30.2-31.9)	31.7 (30.9-32.5)	0.31		
Conscientiousness	29.0 (28.0-30.0)	29.0 (28.1-29.9)	0.95		
Characteristics of BZD use					
Long half-life (%)	17.8	20.0	0.58		
Mean daily dose (mg/day)[1]	4.4 (3.9-4.9)	5.6 (5.0-6.2)	0.001	1.04 (0.63-1.71)	0.89
Duration of use (months)	16.3 (13.3-20.1)	40.9 (33.9-49.4)	<0.001	1.54 (1.26-1.87)	**<0.001**

Table 2. continued

Daily BZD use (%)	28.7	44.0	0.001	1.83 (0.89-3.74)	0.10
Number of different types of BZDs used concomitantly	3.1 (3.1-3.2)	3.1 (3.1-3.2)	0.42		
Benzodiazepine Dependence					
Problematic Use	9.0 (8.6-9.4)	9.7 (9.3-10.1)	0.02	1.09 (0.96-1.24)	0.20
Preoccupation	12.0 (11.5-12.6)	13.4 (12.9-13.9)	0.001	1.04 (0.90-1.19)	0.53
Lack of Compliance	8.7 (8.9.0)	9.4 (9.1-9.6)	0.003	1.05 (0.94-1.18)	0.40
Longitudinal characteristics					
Follow-up time anxiety symptoms (%)			0.04		
No anxiety symptoms	42.6	30.0			
(Less than) half of time symptoms	17.8	19.5		1.39 (0.69-2.80)	0.36
More than half of time symptoms	39.6	50.5		1.21 (0.66-2.21)	0.54
Follow-up time depressive symptoms (%)			0.26		
No depressive symptoms	43.2	35.5			
(Less than) half of time symptoms	2.4	4.0			
More than half of time symptoms	54.4	60.5			
Life Events					
Number of positive life events	1.8 (1.7-2.0)	1.7 (1.5-1.8)	0.17		
Number of negative life events	2.4 (2.1-2.6)	2.6 (2.4-2.9)	0.21		
Switch of treatment setting (%)			0.03		
Always primary care	37.9	50.5			
Exit secondary care	16.0	9.0		0.29 (0.13-0.66)	**0.003**
Entry secondary care	5.3	7.0		0.73 (0.26-2.09)	0.56
Always secondary care	40.8	33.5		0.65 (0.34-1.23)	0.19
Change number chronic illnesses	-0.4 (-0.6 - -0.2)	-0.4 (-0.6 - -0.2)	0.82		
Change Insomnia Rating scale	-3.8 (-4.7 - -2.9)	-2.2 (-3.0 - -1.3)	0.009	1.03 (0.99 – 1.08)	0.14

BZD indicates benzodiazepine; IDS indicates Inventory of Depressive Symptomatology; MDD indicates Major Depressive Disorder; OR indicates odds ratio; CI indicates confidence interval. Means (95% CIs) are given for age, personality characteristics chronic illnesses, pain, personality traits, change in number of chronic illnesses, and change in insomnia rating scale, problematic use, and preoccupation. Geometric means (95% confidence intervals) based on estimated marginal means, calculated by analysis of variance, are presented for education, medical consumption, chronic illnesses, pain, Insomnia Rating Scale, Beck Anxiety Inventory, IDS, daily dosage, duration of use, number of different types of BZDs, and lack of compliance as these values are not normally distributed. Percentages are given for categorical variables. **P* is derived by analysis of variance for quantitative variables or χ^2 statistics for categorical variables. ** P is derived by multivariate logistic regression. All variables with $P < 0.10$ in univariate analyses are entered into the multivariate regression model. The analysis is corrected for sex, age and previous BZD use. Significance is inferred at $P < 0.05$.

DISCUSSION

This longitudinal cohort study aimed to identify the most important predictors of initiated and continued BZD use. In the multivariate model, which included the most consistently identified predictors of BZD use from previous research plus a number of not previously investigated determinants, the following variables appeared to be most important. Initiated BZD use (in nonusers at baseline) was more likely in subjects with insomnia, who had enduring anxiety symptoms, who entered secondary care, and who had used BZDs in the past. It was less likely in subjects who experienced a higher number of positive life events. Continued BZD use (among baseline BZD users) was more likely in older subjects with more severe anxiety and a long baseline duration of BZD use, but less likely in subjects who left secondary care during follow-up.

Regarding the initiation of BZD use, we confirmed previous research, which found that subjects with a history of BZD use were more likely to re-start BZD use due to withdrawal symptoms or a new episode of psychopathology.[37] Furthermore, it was consistent with earlier studies[21] that anxiety and insomnia predicted initiated BZD use and were probably the main reasons to issue new BZD prescriptions. However, the following 4 insights were new: 1) Mainly, subjects who were anxious most of the 2-year follow-up time initiated BZD use, indicating that a short duration of anxiety does not necessarily lead to BZD use. 2) Positive life events were associated with less initiation of BZD use, possibly by alleviation of emotional distress both directly and by buffering the adverse consequences of negative life events.[38] 3) Entry of secondary care increased the likelihood that BZDs were initiated. This might be due to the necessity of adding BZDs to the treatment regime in patients who were referred to secondary care because of unsuccessful primary care treatment. 4) Gender, age, marital status, alcohol abuse, antidepressant use, smoking, physical health, and pain were no independent determinants of initiated BZD use in the current model, although they were in previous research.[12-14] As we

corrected for a broad set of important confounders in our multivariate model, it seems that insomnia, enduring anxiety symptoms, entry into secondary care, and BZD use in the past were more important predictors for the initiation of BZD use than these variables were.

Regarding continuation of BZD use, we confirmed previous research that older age,[14] more severe anxiety,[16] and a longer duration of BZD use in the past[17] were important predictors. Yet, the following 2 findings were new: 1) As compared with primary care patients, subjects who left secondary care during follow-up were more likely to discontinue BZD use, possibly because their mental health status had improved. However, secondary care treatment remained an independent predictor in our model even after adjustment for severity of psychopathology. 2) Continued BZD use was not predicted by gender, marital status, health, pain, living status, GP contacts, insomnia, daily BZD use, potency of BZD, duration of use, BZD dosage, and hypnotic use in our multivariate model, although these variables were important determinants in previous research.[14,15,17,20] Again, as we corrected for a broad set of important confounders in our multivariate model, it seems that severe anxiety, a long baseline duration of BZD use and leaving secondary care during follow-up were more important in the explanation of continuation of BZD use than above described variables were.

Our study had several limitations. Because of the medium sized BZD user group and large number of determinants tested, the power of our study was limited and we were not able to investigate subgroups of users. Furthermore, although participants were asked to bring drug containers to the interview, one fourth of the subjects did not do so. This might have introduced recall bias and some error. Finally, we could not include all previously investigated determinants as some of these were not included in the NESDA study (i.e., stress[12] and life satisfaction[21]). This paper is limited to subject characteristics and does not include interactions with prescribers who also may influence BZD use. There were also several strengths to our study. We were able to include the most consistently

identified determinants of BZD use from cross-sectional and longitudinal research as well as a number of never investigated longitudinal variables in a comprehensive multivariate model. That enabled us to identify the most important independent determinants of initiated and continued BZD use.

In conclusion, this study revealed that insomnia and anxiety were the main reasons for initiated BZD use, whereas older age and anxiety were the main reason for continued BZD use. Gender, education, pain, and physical health appeared to be less important.

REFERENCES

1. Lader MH. Limitations on the use of benzodiazepines in anxiety and insomnia: are they justified? *European Neuropsychopharmacology*. 1999;9:399-405.
2. Hollister LE, Mulleroerlinghausen B, Rickels K, et al. Clinical Uses of Benzodiazepines. *Journal of Clinical Psychopharmacology*. 1993;13:S1-S169.
3. Woods JH, Katz JL, Winger G. Benzodiazepines - Use, Abuse, and Consequences. *Pharmacological Reviews*. 1992;44:151-347.
4. Woods JH, Winger G. Current Benzodiazepine Issues. *Psychopharmacology*. 1995;118:107-115.
5. Perodeau G, Cappeliez P. Quality of life and benzodiazepine drug use by community-dwelling elderly: a stress and coping perspective. *European Review of Applied Psycholo*gy 2007;57:193-200.
6. Neutel CI. The epidemiology of long-term benzodiazepine use. *International Review of Psychiatry*. 2005;17:189-197.
7. Donoghue J, Lader M. Usage of benzodiazepines: A review. *International Journal of Psychiatry in Clinical Practice*. 2010;14:78-87.
8. Shader RI, Greenblatt DJ. Drug-Therapy - Use of Benzodiazepines in Anxiety Disorders. *New England Journal of Medicine*. 1993;328:1398-1405.
9. 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.
10. Terluin B, van Heest F, van der Meer K, et al. NHG-Standaard Angststoornissen (eerste herziening). *Huisarts Wet*. 2004;47:26-37.
11. Manthey L, van VT, Giltay EJ, et al. Correlates of (inappropriate) benzodiazepine use: the Netherlands Study of Depression and Anxiety (NESDA). *Br J Clin Pharmacol*. 2011;71:263-272.
12. Boeuf-Cazou O, Niezborala M, Marquie JC, et al. Factors associated with psychoactive drug initiation in a sample of workers in France: results of the VISAT cohort study. *Pharmacoepidemiology and Drug Safety*. 2010;19:296-305.

13. Bartlett G, Abrahamowicz M, Grad R, et al. Association between risk factors for injurious falls and new benzodiazepine prescribing in elderly persons. *Bmc Family Practice*. 2009;10:1.
14. Luijendijk HJ, Tiemeier H, Hofman A, et al. Determinants of chronic benzodiazepine use in the elderly: A longitudinal study. *British Journal of Clinical Pharmacology*. 2008;65:593-599.
15. Jorm AF, Grayson D, Creasey H, et al. Long-term benzodiazepine use by elderly people living in the community. *Australian and New Zealand Journal of Public Health*. 2000;24:7-10.
16. Dealberto MJ, Seeman T, Mcavay GJ, et al. Factors related to current and subsequent psychotropic drug use in an elderly cohort. *Journal of Clinical Epidemiology*. 1997;50:357-364.
17. Gray SL, Eggen AE, Blough D, et al. Benzodiazepine use in older adults enrolled in a health maintenance organization. *American Journal of Geriatric Psychiatry*. 2003;11:568-576.
18. 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.
19. 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.
20. Barnas C, Whitworth AB, Fleischhacker WW. Are Patterns of Benzodiazepine Use Predictable - A Follow-Up-Study of Benzodiazepine Users. *Psychopharmacology*. 1993;111:301-305.
21. Fourrier A, Letenneur L, Dartigues JF, et al. Benzodiazepine use in an elderly community-dwelling population - Characteristics of users and factors associated with subsequent use. *European Journal of Clinical Pharmacology*. 2001;57:419-425.
22. 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.
23. Penninx BW, Beekman AT, Smit JH, et al. The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and methods. *Int J Methods Psychiatr Res*. 2008;17:121-140.

24. Penninx BWJH, Nolen WA, Lamers F, et al. Two-year course of depressive and anxiety disorders: Results from the Netherlands Study of Depression and Anxiety (NESDA). *Journal of Affective Disorders:* 2011; 133: 76-85.
25. Riss J, Cloyd J, Gates J, et al. Benzodiazepines in epilepsy: pharmacology and pharmacokinetics. *Acta Neurologica Scandinavica*. 2008;118:69-86.
26. WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD System 2009.
27. Beck AT, Epstein N, Brown G, et al. An inventory for measuring clinical anxiety: psychometric properties. *J Consult Clin Psychol*. 1988;56:893-897.
28. 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.
29. Wardenaar KJ, van VT, 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;125:146-154.
30. Pearlin LI, Schooler C. Structure of Coping. *Journal of Health and Social Behavior*. 1978;19:2-21.
31. Costa PT, McCrae RR. Domains and facets: hierarchical personality assessment using the revised NEO personality inventory. *Journal of Personality Assessment*. 1995;64:21-50.
32. Roijen Lv, Straten Av, Tiemens B, et al. Handleiding Trimbos/iMTA questionnaire for costs associated with psychiatric illness (Tic-P). 2002.
33. VonKorff M, Ormel J, Keefe FJ, et al. Grading the Severity of Chronic Pain. *Pain*. 1992;50:133-149.
34. Babor TF, Kranzler HR, Lauerman RJ. Early Detection of Harmful Alcohol-Consumption - Comparison of Clinical, Laboratory, and Self-Report Screening Procedures. *Addictive Behaviors*. 1989;14:139-157.
35. Lyketsos CG, Nestadt G, Cwi J, et al. The Life Chart Interview: A standardized method to describe the course of psychopathology. *International Journal of Methods in Psychiatric Research*. 1994;4:143-155.
36. Brugha T, Bebbington P, Tennant C, et al. The List of Threatening Experiences - A Subset of 12 Life Event Categories with Considerable Long-Term Contextual Threat. *Psychological Medicine*. 1985;15:189-194.

37. Zitman FG, Couvee JE. Chronic benzodiazepine use in general practice patients with depression: an evaluation of controlled treatment and taper-off - Report on behalf of the Dutch Chronic Benzodiazepine Working Group. *British Journal of Psychiatry*. 2001;178:317-324.

38. Davidson L, Shahar G, Lawless MS, et al. Play, pleasure, and other positive life events: "Non-specific" factors in recovery from mental illness? *Psychiatry-Interpersonal and Biological Processes*. 2006;69:151-163.