

# Determinants of chronic benzodiazepine use in the elderly: A longitudinal study

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## WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- The risk of adverse events due to chronic benzodiazepine use is high in the elderly.
- Cross-sectional studies have shown that increasing age, female gender and poor physical and mental health are associated with benzodiazepine use.
- When users were re-examined some years later, chronic somatic disease, pain and stress seemed to contribute to the continuation of benzodiazepine use.

## WHAT THIS STUDY ADDS

- This is the first longitudinal study that analyzed the determinants of new-onset chronic benzodiazepine use in community-dwelling elderly.
- Symptoms of depression, hypertension, pain related joint complaints and the perception of poor physical health predicted new-onset chronic use. Living alone was found to decrease the risk of chronic use.

## AIMS

The risk of adverse events due to chronic benzodiazepine use is high in the elderly. Clinicians need to be able to identify those persons who are at risk of chronic benzodiazepine use, but little is known about the determinants. This study determined social and health related factors that predict new-onset chronic benzodiazepine use in community-dwelling elderly.

## METHODS

This study was embedded in an ongoing cohort study among 5364 persons aged  $\geq 57$  years. Drug-dispensing medication records were available for the period between 1991 and 2003. We defined chronic benzodiazepine use as use during at least 180 days in a period of 365 consecutive days. The association of various social, psychiatric and somatic variables with new-onset chronic benzodiazepine use was studied with a Cox proportional hazards analysis.

## RESULTS

Symptoms of depression, hypertension, pain related joint complaints and the perception of poor physical health predicted new-onset chronic use. In the subsample of participants who had filled at least one prescription in the follow-up period, of these variables only pain related joint complaints increased the risk of new-onset chronic use. Living alone protected against chronic benzodiazepine use.

## CONCLUSIONS

The elderly with poor mental and physical health are at an increased risk of chronic benzodiazepine use. Living alone was found to decrease the risk of chronic use, which suggests that social factors may determine drug usage patterns. Very few characteristics predicted chronic benzodiazepine use once patients had received their first prescription. For clinicians, identification of patients at high risk is therefore not straightforward.

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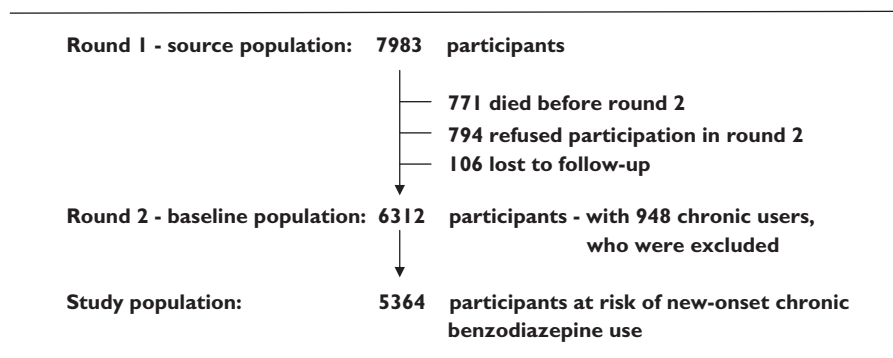
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**Figure 1**

Flow diagram of study population

established by self-report. We used history of myocardial infarction, cerebrovascular accidents, hypertension, and current pain related joint complaints as determined by self-report.

The third domain involved participants' health perception and behaviour. Firstly, we used a measure of Activities of Daily Living based on the Modified Stanford Health Assessment Questionnaire [14]. Secondly, we determined subjective health by asking participants to rate their health as worse, same or better than that of peers. Self-reported alcohol use and smoking were categorized into none, former, and current.

In addition to these three domains, participants' demographic characteristics, i.e. age, sex, highest education attained, and health insurance were taken into account.

### Data analysis

We performed two Cox proportional hazards analyses. In these analyses each participant contributed person-years from the date of the baseline interview until follow-up ended either with the event of chronic use or when a participant was censored due to death, loss-to-follow, or the end of study on January 1, 2003. First, we compared the social and health related characteristics of new-onset chronic benzodiazepine users with those of all other participants. We thus aimed to clarify which characteristics increase the risk of chronic use in the general population. We performed the second analysis in the subsample of participants who had filled at least one prescription for a benzodiazepine during the follow-up period. In this way, we analyzed which characteristics increase the risk of new-onset chronic use in the group of benzodiazepine users, i.e. which users go on to become chronic users.

For each analysis, we determined whether the social and health related factors were associated with new-onset chronic benzodiazepine use by calculating the hazard rates adjusted for age and sex. The factors with a  $P < 0.10$  in the age and gender adjusted model were included in the

final model. The factors with a  $P$  value  $< 0.05$  in the final multivariate analysis were considered to be determinants of chronic use.  $P$  values are two-sided and were considered statistically significant if less than 0.05. We used SPSS 11.0 to perform the analyses.

## Results

We identified 440 new cases of chronic benzodiazepine use in 39 164 person-years. Thus, of the 2490 participants who had filled at least one prescription for a benzodiazepine, 17.7% became chronic users during the follow-up period, which was on average 7.3 years. Table 1 displays the baseline characteristics of the study population. Table 2 describes the type, half-life and daily dosages in terms of defined daily dosage (DDD) of the benzodiazepines first prescribed and of the benzodiazepines that the chronic users used at the index date. Note that 21 chronic users used two and one chronic user used three different benzodiazepines concurrently.

Table 3 shows the independent determinants of new-onset chronic benzodiazepine use in bold. Note that the hazard rates (HR) in Table 3 were not adjusted for anxiety and hours of sleep because missing values for these variables exceeded 20%. The hazard rates for anxiety and sleep, as shown in Table 3, were derived from separate Cox proportional hazard analyses for the groups of participants for which these variables were known (complete case analysis). Increasing age, female gender, public health insurance, depressive complaints, less than 6 h of sleep per night, hypertension, pain related joint complaints, poor subjective health, and current smoking predicted new-onset chronic benzodiazepine use. Living alone was a protective factor against new-onset chronic benzodiazepine use. An analysis stratified for gender showed that this protective effect was quite similar in men (HR 0.55; 95% CI 0.29, 1.02) and women (HR 0.71; 95% CI 0.55, 0.93).

**Table 1**

Baseline characteristics of the study population

Characteristic	n = 5364
<b>Patient characteristics</b>	
<i>Socio demographic variables</i>	
Age (years, mean (range))	70.2 (56.5–101.8)
Gender (% female)	56.6
Primary school only (%)	20.6
Public health insurance (%)	52.5
<i>Social support</i>	
<i>Living situation</i>	
With partner or other person (%)	72.0
Alone (%)	28.0
Number of children (mean (range))	2.1 (0–16)
<i>Place of residence</i>	
Independently (%)	87.8
Service flat (%)	8.3
Home for the elderly (%)	4.0
<i>Psychiatric and physical health</i>	
Anxiety (% HADS-A ≥ 8)*	11.3
Depression (% HADS-D ≥ 8 or CES-D ≥ 16)†	10.9
MMSE (% < 26)	10.0
Sleep (% < 6 h)	6.7
Myocardial infarction (%)	8.0
Stroke (%)	1.6
Hypertension (%)	35.0
Joint or back complaints (%)	18.6
<i>Other patient characteristics</i>	
Activities of daily living (mean score (range))‡	1.29 (1.00–4.00)
<i>Subjective health (%)</i>	
Better	54.1
Same	38.3
Worse	7.7
<i>Alcohol use (%)</i>	
Nonuser	24.7
Former user	0.9
Current user	74.4
<i>Smoking (%)</i>	
Nonsmoker	30.9
Former smoker	49.9
Current smoker	19.2

\*Hospital Anxiety and Depression Scale (HADS) known for 2580 participants.

†Center for Epidemiologic Studies Depression Scale (CES-D) known for 1629. ‡A score of 1.5 or lower indicates independent functioning.

The results of the second analysis, in the subsample of participants who had filled at least one benzodiazepine prescription, are provided in Table 4. Female gender, depressive complaints, hypertension and current smoking were no longer associated with new-onset chronic use. Only, increasing age, public health insurance and pain related joint complaints predicted new-onset chronic benzodiazepine use in those who had filled at least one prescription. Again, living alone was associated with a decreased risk of benzodiazepine use. *Post-hoc* we analyzed whether a hypnotic or anxiolytic as the first benzodiazepine is associated with the risk of chronic use and found that, while adjusting for age and sex, a hypnotic first benzodiazepine increased the risk of chronic use compared with an anxiolytic first benzodiazepine (HR 1.39; 95% CI 1.15, 1.68).

## Discussion

In this prospective study, we analyzed social and health related risk factors of new-onset chronic benzodiazepine use in an older community-dwelling population. Symptoms of depression, hypertension, pain related joint complaints, and the perception of poor physical health were associated with an increased risk of chronic benzodiazepine use. However, in the subsample of participants who had filled at least one prescription, having pain related joint complaints was the only health related risk factor associated with new-onset chronic benzodiazepine use. In both population samples, increasing age, and public health insurance increased the risk of chronic benzodiazepine use, and living alone reduced the risk of new-onset chronic use.

To our knowledge, we present the first prospective study which has established that both social and health related patient characteristics determine new-onset chronic benzodiazepine use in elderly people. There are two other longitudinal studies that investigated risk factors of new-onset chronic benzodiazepine use in an older, general population, but these were limited by their design [1, 15]. In the study by Egan *et al.* the number of cases was small ( $n = 18$ ), so that lack of power may explain that the risk of chronic use was not associated with health status, cognitive status, and anxiety, but with increasing age only [1]. The other study, by Simon *et al.* did not take somatic or psychological health status into account [15].

Several follow-up studies of elderly users have been published. They analyzed the risk factors for chronic benzodiazepine use in older people who were users already; in other words, risk factors for continuous, not new-onset, chronic use were studied [5–9, 16]. In these studies, neither anxiety, depressive symptoms, cognitive impairment, nor chronic somatic diseases were related to an increased risk of continuous chronic use [6, 7, 9], although having a chronic somatic disease or pain did show a positive association [5, 8]. We also found a relationship with pain related joint complaints in the participants who had filled at least one prescription. This is a disturbing finding, not only because pain related joint complaints, like benzodiazepine use, increase the risk of falls, but also because pain is managed more effectively with analgesics. Moreover, not only are pain related joint complaints related to chronic use, they are often the primary reason for initiating the treatment, as shown by the chart review of Simon *et al.* [15].

Contrary to our hypothesis that living with a partner or other person would be associated with a reduced risk of new-onset chronic benzodiazepine use, living alone protected against chronic use. Several explanations are conceivable, if this is not a chance finding. First, a person who lives alone does not adjust his sleeping pattern to that of someone else. Responding to the stimuli of one's own circadian rhythm is probably beneficial for one's night's rest.

**Table 2**

Characteristics of benzodiazepine prescriptions

	All users (n = 2490)	Chronic users (n = 440)
<b>First benzodiazepine prescription</b>		
Type of benzodiazepine		
Anxiolytic (%)	58.8	50.0
Hypnotic/sedative (%)	41.2	50.0
Daily dosage		
Mean	0.30	
≤0.5 DDD* (%)	67.4	63.4
0.5–1.0 DDD (%)	28.8	32.7
>1.0 DDD (%)	4.0	3.9
Half-life		
Short (%)	67.6	69.6
Long (%)	32.4	30.4
<b>Benzodiazepine prescription at index date</b>		
Type of benzodiazepine†		
Anxiolytic (%)	–	48.4
Hypnotic/sedative (%)	–	55.9
Daily dosage‡		
Mean	–	0.61
≤0.5 DDD‡ (%)	–	69.9
0.5–1.0 DDD (%)	–	24.0
>1.0 DDD (%)	–	6.1
Half-life‡		
Short (%)	–	80.7
Long (%)	–	20.9

\*DDD stands for defined daily dosage (this is the recommended daily dosage for an adult of 70 kg). †Percentages do not add up to 100% because 22 chronic users used more than one benzodiazepine at the index date. ‡In chronic users who used more than one benzodiazepine DDDs were added.

Secondly, living alone may be an indicator of good health. Although we adjusted for various psychiatric and somatic factors the possibility of residual confounding cannot be ruled out. Thirdly, one could argue that persons who live alone pay less attention to a sleeping disorder. However, even in those who filled at least one benzodiazepine prescription, and therefore must have discussed this problem with a physician, living alone was protective against chronic use as well. Previous studies that analyzed the role of living alone or marital status found no association with continuous benzodiazepine use [6–9].

With respect to demographic risk factors, two issues need to be discussed. First, a common perception, based on findings from cross-sectional studies, is that the risk of using benzodiazepines increases with age [17–19]. Our study and the other prospective study adjusting for health status also found that age increased the risk of new-onset chronic use in the general elderly population [1]. This also applied to the subsample of participants who filled at least one prescription. On the other hand, the follow-up studies among users did not find an increasing risk with age, even if they adjusted for health status as well [5, 7–9]. Age seems to be an independent risk factor for new-onset chronic benzodiazepine use, but not for continuing chronic use. This inconsistency in results could be due to different prescription patterns in the different samples. Follow-up studies of benzodiazepine users cannot rule out that the

different age groups already have different usage patterns at baseline. For example, younger persons may be more likely than elderly persons to be either nonusers or chronic users.

Another common perception derived from cross-sectional studies is that female sex increases the risk of chronic use [17–19]. We found that female gender was associated with an increased risk in the general population, but this relationship no longer existed in the subsample of participants who filled at least one prescription. This is consistent with many other studies among users [5, 6, 9, 16]. Thus, neither male nor female gender increases the risk to continue benzodiazepine use once a person has begun. The explanation for the predominance of females among chronic users must therefore lie in their high rate to start benzodiazepine use. This suggests that the threshold to begin, not difficulty to stop, is gender related.

Our study has several strengths. A prospective design was combined with a rigorous selection of the study population. Participants who were already chronic users at baseline were carefully identified, using a prebaseline selection period of 2 years. In addition, benzodiazepine use was registered on a continuous basis and the follow-up of 10 years was relatively long. Both contributed to an accurate identification of new-onset chronic use. Although utilization data are more precise than prescription data, we consider day-to-day prescription data more precise than retrospec-

**Table 3**

Determinants of chronic benzodiazepine use in older people (n = 5364)

Variable	Hazard rate* (95% CI)
<i>Socio-demographic variables</i>	
Age (years)	1.04 (1.03, 1.06)
Female	1.67 (1.31, 2.14)
Public health insurance	1.23 (1.01, 1.51)
<i>Social support</i>	
Living situation	
With partner or other person	1.00 (reference)
Alone	0.66 (0.52, 0.84)
Place of residence	
Independently	1.00 (reference)
Service flat	1.34 (0.98, 1.83)
Home for the elderly	0.72 (0.36, 1.42)
<i>Psychiatric and physical health</i>	
Anxiety (n = 2580) HADS-A ≥ 8	1.46 (0.98, 2.19)
Depression HADS-D ≥ 8 or CES-D ≥ 16	1.53 (1.14, 2.07)
Sleep (n = 2104), <6 h	1.66 (1.08, 2.54)
Myocardial infarction	1.18 (0.83, 1.67)
Hypertension	1.29 (1.05, 1.57)
Pain related joint complaints	1.45 (1.16, 1.81)
<i>Other patient characteristics</i>	
Activities of daily living per score	1.00 (0.81, 1.24)
Subjective health	
Better	1.00 (reference)
Same	1.09 (0.88, 1.34)
Worse	1.50 (1.06, 2.13)
Alcohol	
None	1.00 (reference)
Former	0.94 (0.30, 2.97)
Current	0.86 (0.68–1.07)
Smoking	
None	1.00 (reference)
Former	0.92 (0.71, 1.19)
Current	1.36 (1.01, 1.82)

\*Cox proportional hazards analysis. CESD, Center for Epidemiologic Studies Depression Scale; HADS, Hospital Anxiety and Depression Scale. Numbers in bold indicate independent determinants of new-onset chronic benzodiazepine use.

tive self-reported use on which the follow-up studies among users have been based.

Following the recommendations of Zandstra *et al.* [2], we chose a quantitative instead of clinical, DSM-IV based definition of chronic benzodiazepine use. Most elderly benzodiazepine users do not show signs of dependence such as escalation of dose, withdrawal symptoms, or detrimental effects on health and daily life [20]. It is the chronic use of benzodiazepines, not just the misuse, which may result in adverse events in the elderly, such as fractures.

A limitation of this study was that anxiety and depressive complaints could not be classified according to the DSM-IV. Moreover, we only had information on complaints of anxiety in a subsample of participants. This limited our power to detect an association between anxiety and new-onset chronic benzodiazepine use. Also, we could not take into account perceived social support, personality disorders, or attitudes towards benzodiazepine use [21].

Given that 17.7% of the users in our cohort proceeded to chronic benzodiazepine use after the first prescription,

**Table 4**

Determinants of chronic benzodiazepine use in older users\* (n = 2490)

Variable	Hazard rate† (95% CI)
<i>Socio-demographic variables</i>	
Age (years)	1.04 (1.03, 1.06)
Female	1.15 (0.90, 1.47)
Public health insurance	1.24 (1.01, 1.51)
<i>Social support</i>	
Living situation	
With partner or other person	1.00 (reference)
Alone	0.73 (0.58, 0.93)
Place of residence	
Independently	1.00 (reference)
Service flat	1.41 (1.04, 1.92)
Home for the elderly	1.50 (0.78, 2.89)
<i>Psychiatric and physical health</i>	
Depression, HADS-D ≥ 8 or CES-D ≥ 16	1.22 (0.91, 1.64)
Hypertension	1.11 (0.91, 1.35)
Pain related joint complaints	1.32 (1.06, 1.64)
<i>Other patient characteristics</i>	
Subjective health	
Better	1.00 (reference)
Same	1.05 (0.86, 1.29)
Worse	1.34 (0.96, 1.87)
Alcohol	
None	1.00 (reference)
Former	0.84 (0.26, 2.65)
Current	0.82 (0.66, 1.03)
Smoking	
None	1.00 (reference)
Former	0.88 (0.68, 1.15)
Current	1.21 (0.90, 1.62)

\*The subsample of participants who filled at least one prescription. †Cox proportional hazards analysis. Numbers in bold indicate independent determinants of new-onset chronic benzodiazepine use.

this first prescription implies a substantial risk to become a chronic user. A number of demographic, social and health related patient characteristics predicted new-onset chronic benzodiazepine use in the general elderly population, but very few characteristics predicted chronic use once patients had received their first prescription. As it is difficult to identify the patients who are at risk of chronic use, this group cannot be targeted with specific prevention programs. This further supports the already existing recommendations to be very prudent with initiating benzodiazepine therapy in older people. Finally, our finding that living alone protects against chronic benzodiazepine use indicates that more awareness is needed for the role of social patient characteristics in the development of chronic benzodiazepine use.

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