Anxiety, Depression and Cognition in Later Life

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2008

document version
Publisher's PDF, also known as Version of record

Chapter 6

Ten-Year trends in benzodiazepine use in the Netherlands

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Submitted for publication.

Abstract

***Objective**: The aim of this study was to assess trends in benzodiazepine use in later life. It was hypothesized that benzodiazepine use decreases due to increasing knowledge on adequate treatment of affective problems and awareness of the negative consequences of prolonged benzodiazepine use in older people. **Method**: Data from the Longitudinal Aging Study Amsterdam were used to investigate trends in benzodiazepine use between 1992 and 2002 in two population-based samples aged 55-64 years. Differences between the two cohorts with respect to benzodiazepine use, and sociodemographic, and physical and mental health characteristics were tested with chi-square tests, t-tests for independent samples and logistic regression analyses. **Results**: Benzodiazepine use remained stable over ten years. In the subgroups shifts in benzodiazepine use were found but these differences were not statistically significant. **Conclusion**: Overall benzodiazepine use in this older population sample remained stable from 1992 to 2002. A decrease of benzodiazepine use, as was expected based on the increasing insights in the serious consequences of prolonged benzodiazepine use, was not found. It is recommended to pay special attention to benzodiazepine users with, often long-standing, physical and mental health problems.*

Introduction

There is widespread concern about benzodiazepine use in older people. Benzodiazepines have several adverse effects, particularly in older people, such as an increased risk of falling due to the sedative effects (1) and a negative effect on cognitive functioning (2). In case of a depressive disorder, it can worsen the depressive symptoms (3) and when used for a longer period (more than two months) benzodiazepine use may lead to addiction problems, with withdrawal symptoms, diminishing effect and difficulty in discontinuing treatment (4). However, benzodiazepines are widely used by older people (5-9) in the treatment of anxiety complaints, nervousness and sleeping problems. Furthermore, despite the generally accepted advice to keep treatment short, benzodiazepines are often prescribed for long periods of time, also in older persons (9).

In the past decades depression and anxiety disorders in older people have come under study, leading to increasing emphasis on the importance of adequate treatment of these disorders. The newer generation of antidepressants, the selective serotonine reuptake inhibitors (SSRI's), which are used in the treatment of depression as well as anxiety disorders, have become very popular and their use has shown a huge increase in the past decades, also in older people (10,11). Also, the impact of side effects and addiction problems of benzodiazepines has lead to the recommendation of short-term prescription and discontinuing use where possible, particularly in older people, with a preference for the short working benzodiazepines. Thus, it might be expected that benzodiazepine use decreased in the past years due to improved medical practice. Other developments that may lead to a decrease in benzodiazepine use is an increase of interest in and knowledge on physical and mental health issues in the general population in the past decades through the mass media and the more open communication. This has led to an increasing awareness of positive and negative consequences of drug use and an enhanced participation of patients in the process of medical decision-making. Although this development might lead to a decrease of benzodiazepine use, it may also have an opposite effect due to the addictive properties of these drugs.

In the present study it is investigated whether this increase in knowledge and sharing of information has lead to a more adequate application and usage of benzodiazepines in older people. As far as we know trends in benzodiazepine use in older people have not been investigated yet. Our hypothesis is that in the past decades benzodiazepine use has decreased, because of the more specific guidelines concerning duration and discontinuing of treatment and the increasing public knowledge of the impact of the negative effects. We will investigate this in a large epidemiological study taking age, gender, income, education, physical

problems, cognition, depression, anxiety, sleeping problems, antidepressant use and alcohol use, into consideration.

Methods

Sampling and procedures

Data were derived from the Longitudinal Aging Study Amsterdam (LASA), a longitudinal, interdisciplinary study on the predictors and consequences of changes in autonomy and well-being in the aging population (12). Sampling procedures and characteristics of the sample have been described in detail in previous publications (13-15). In short, the LASA cohort is based on a representative random sample of older adults between the ages of 55 and 85, stratified for age, gender and expected mortality five years into the study. The sample was drawn from the population registers of 11 municipalities in three regions of the Netherlands. Ten months prior to the LASA-baseline, the sample was used in another study (Living arrangements and Social Networks of older adults (LSN)), with a response of 62.3% (16). Of the 3,805 LSN-participants, 81.7% (n = 3,107) participated in LASA. Attrition between LSN and the first LASA-cycle was due to mortality (3.3%), refusal (10.4%), serious physical illness or cognitive impairment (3.5%) and failure to contact (1.2%). Non-response in the first LASA-cycle was related to age, but not to gender. Data-collection in LASA started in 1992-1993 (LASA-baseline) and participants were questioned every 3 years ever since.

In 2002/2003 a new population sample was drawn, called LASA-2, by using comparable sampling procedures to LASA-1. LASA-2 consisted of 1,002 respondents, with ages ranging from 55 to 65.

To address our research question, changes in benzodiazepine use in ten years, respondents of equal ages (55-64 years) from both cohorts were selected, resulting in 966 (LASA-1) and 1,002 (LASA-2) participants. Due to non-response on benzodiazepine use, samples of n = 874 (LASA-1) and 919 (LASA-2) were available for the analyses. In both cohorts this non-response was not related to age, gender, or the other covariates.

All interviews were conducted in the homes of respondents, by specifically trained and intensively supervised interviewers. Informed consent was obtained from each respondent, according to the prevailing legal requirements. The study was approved by the Medical Ethical Committee of the VU University Medical Centre.

Measures

Use of benzodiazepines.

Use of prescribed drugs was assessed in LASA-1 and LASA-2 by recording the medication directly from the drug containers in the home of the respondents. The anatomical-therapeutical-chemical (ATC) coding and categorization system for drug data coding (17) was used to classify all medication. Benzodiazepines were categorised as tranquillising agents (anxiolytics) or sleeping pills (hypnotics). Separate nominal variables were computed, indicating the use of anxiolytic drugs or hypnotic drugs (coded as 'yes' or 'no').

Covariates

Gender was investigated as a covariate, because of the preponderance of women in benzodiazepine use (18), and in the prevalences of depression and anxiety disorders (19,20). Because *socio-economic status* is known to be associated with health status and health behavior, the level of education and the level of income were included as independent variables.

The *level of education* was classified in three levels: low education (elementary not completed, elementary education), medium education (lower vocational education, general intermediate education, intermediate vocational education, general secondary education), and high education (higher vocational education, college education and university education). *Income* was classified in three levels: low income (less than 1000 Euros per month), intermediate income (1000-3000 Euros per month) and high income (more than 3000 Euros per month). Income in LASA-1 was corrected for inflation of 3% per year.

Impaired *physical health* is associated with depression and anxiety complaints. Therefore chronic disease and functional limitations were included as independent variables.

Chronic disease was assessed using a detailed questionnaire on the following chronic diseases: chronic non-specific lung disease, cardiac disease, peripheral atherosclerosis, stroke, diabetes mellitus, arthritis, malignant neoplasms, or any other chronic diseases. The total number of diseases ranged from 0 to 12. These data were cross-checked with the General Practitioners of the participants. Accuracy of self-report was shown to be independent of cognitive impairment, level of depressive symptoms and anxiety symptoms (21).

Functional limitations were measured with a questionnaire on difficulty experienced with several activities (walking up and down stairs, using public transportation and cutting own toenails). This questionnaire was validated in the Netherlands by Van Sonsbeek (22) and Kriegsman et al (23).

Cognitive impairment might hamper recognition and treatment of affective disorders, but it also can be a side effect of benzodiazepine use. It was measured with the Mini-Mental Status Examination (MMSE), a frequently used screening instrument for global cognitive functioning. Scores range from 0 to 30 with higher scores indicating better cognitive performance. We used the cut-off score of 23 (24) to indicate cognitive impairment.
Excessive *alcohol consumption* may be an indication for addiction problems, but it also can be used as self-medication in the case of withdrawal symptoms in excessive benzodiazepine use. Alcohol consumption was assessed with a questionnaire developed for the Netherlands Health Interview Survey (25) and classified according to the Garretsen Index of Present Alcohol Use (26), into three categories (excessive/severe, moderate/light and non-drinker).
Depressive symptoms, anxiety symptoms and sleeping problems, often the reason for benzodiazepine use, were measured with the Centre for Epidemiologic Studies Depression Scale (CES-D), a 20-item self-report scale developed for use in the community (27-29). The CES-D ranges from 0 to 60 with higher scores indicating more depressive symptoms. The dichotomous score based on the commonly used cut-off score of 16 was used (30) to indicate clinically relevant depressive symptoms. Although the CES-D is particularly made for the screening of depressive symptoms, it may also be used as a screener of anxiety symptoms. We used the particular CES-D item about feelings of nervousness and tension (item number 10: feeling fearful) to measure *anxiety*.
To investigate *sleeping problems* we used CES-D item number 11 (sleep being restless).
Antidepressant use was measured in the same way as benzodiazepine use, i.e. based on information on the drug containers, provided by the respondents. A separate nominal variable was computed, indicating the use of antidepressant drugs, coded as ‘yes’ or ‘no’.

Statistical analyses

Because age and gender were not equally distributed in the two cohorts, a weighing procedure was performed, with LASA-1 used as the reference. Details of this procedure are described in another publication (31). To investigate the differences in benzodiazepine use between LASA-1 and LASA-2, i.e. to make a comparison between the two cohorts possible, we pooled the data from both cohorts and added the factor ‘time’ by defining the variable ‘cohort number’ (1 = LASA-1 and 2 = LASA-2). In this pooled data file the differences between LASA-1 and LASA-2 with respect to benzodiazepine use and all covariates were measured and tested with chi-square tests and t-tests for independent samples. To investigate differences in benzodiazepine use between the cohorts, the association between cohort and

benzodiazepine use was studied in logistic regression analyses adjusted for the covariates, with benzodiazepine use as the dependent variable. In the chi-square tests, the t-tests and the logistic regression analyses, *p*- values lower than 0.05 were regarded as statistically significant. To investigate effect modification of the covariates on the cohort differences in benzodiazepine use, logistic regression analyses with interaction-terms of cohort with the covariates were performed. In these analyses *p*-values lower than 0.10 were regarded as statistically significant. Statistical analyses were performed with SPSS, version 12.0.1.

Results

An overview of the characteristics and the differences between LASA-1 and LASA-2 is shown in table 1. Benzodiazepine use in LASA-1 and LASA-2 showed no major difference, nor did separate rates of tranquillising agents and sleeping pills.

Table 1. Socio-demographic characteristics, physical and mental health and benzodiazepine use in LASA-1 and LASA-2, weighed by age and gender.

	LASA-1 **N = 874**		**LASA-2** **N = 919**		*Cohort differences P-value*
	N	%	*N*	%	
Gender:					
Male	419	47.9 %	434	47.2 %	p = 0.76
Female	455	52.1 %	485	52.8 %	
Age group:					
55-59	405	46.2 %	456	49.6 %	p = 0.17
60-64	469	53.7 %	463	50.4 %	
Education:					
Low	268	30.7 %	188	20.5 %	**p= 0.00**
Intermediate	479	54.8 %	532	57.9 %	
High	127	14.5 %	199	21.7 %	
Income:					
Low	135	15.4 %	100	10.9 %	**p= 0.00**
Medium	370	42.3 %	365	39.7 %	
High	211	24.1 %	375	40.8 %	
No answer	158	18.1 %	79	8.6 %	
Chronic diseases:					
None	310	35.5 %	243	26.4 %	**p= 0.00**
One or more	564	64.5 %	676	73.6 %	
Functional limitations (of #3):					
None	725	83.0 %	667	72.6 %	**p= 0.00**
One or more	149	17.0 %	252	27.4 %	
Cognitive impairment:					
No: MMSE > 23	848	97.0 %	888	96.6 %	p = 0.52
Yes: MMSE ≤ 23	26	3.0 %	31	3.4 %	

Depression:					
No	781	89.4 %	790	86.0 %	**p= 0.03**
Yes (CESD ≥ 16)	93	10.6 %	129	14.0 %	
Anxiety: being fearful					
No	785	89.8 %	803	87.4 %	p = 0.16
Sometimes - often	89	10.2 %	116	12.6 %	
Sleeping problems:					
Never / some of the time	753	86.2 %	758	82.5 %	**p= 0.03**
Occasionally - often – always	121	13.8 %	161	17.5%	
Use of alcohol:					
Never	129	14.8 %	75	8.2 %	**p= 0.00**
Light – moderate	683	78.1 %	744	80.9 %	
(very) excessive	62	7.1 %	100	10.9 %	
Antidepressant use:					
No	861	98.5 %	883	96.1 %	**p= 0.00**
Yes	13	1.5 %	36	3.9 %	
Benzodiazepine use:					
All	68	7.8 %	73	7.9 %	p = 0.90
Anxiolytics	32	3.7 %	44	4.8 %	p = 0.24
Hypnotics	40	4.6 %	36	3.9 %	p = 0.49

As a consequence of the weighing procedure, age per year and gender were equally distributed in the two cohorts. Comparing the two birth-cohorts, the later cohort was higher educated and had a higher income. Further, respondents in LASA-2 reported more chronic diseases and functional limitations, and showed more depressive symptoms. They also reported more sleeping problems. Cognitive impairment and anxiety symptoms remained rather stable in the two cohorts. In LASA-2 more respondents used alcohol. Furthermore, there was a remarkable increase of antidepressant use.

Although overall benzodiazepine use did not differ between LASA-1 and LASA-2, cohort differences in benzodiazepine use might be expected for the socio-demographic and health characteristics. Therefore we investigated cohort differences in benzodiazepine use in the subgroups of these characteristics (table 2). Although an increase of benzodiazepine use was found in several groups (e.g. in females, and in respondents with low education, low income, depression, anxiety complaints and sleeping problems), and a decrease in other groups (e.g. in males, and in respondents with high education, high income and with an antidepressant) these differences were not statistically significant, probably due to the small numbers in several subgroups.

Table 2. Benzodiazepine use by socio-demographic and health measures in LASA-1 and LASA-2, weighed by age and gender.

	LASA-1 N = 874		**LASA-2 N = 919**		*Cohort differences*
	Benzodiazepine users:		**Benzodiazepine users:**		
Subgroups:	*N*	*% in subgoup*	*N*	*% in subgroup*	*P-value*
Gender:					
males	21	5.0 %	14	3.2 %	p = 0.19
females	47	10.3 %	59	12.2 %	p = 0.37
Age group:					
55-59	30	7.4 %	35	7.7 %	p = 0.88
60-64	38	8.1 %	38	8.2 %	p = 0.95
Education:					
Low	25	9.3 %	22	11.7 %	p = 0.41
Intermediate	34	7.1 %	44	8.3 %	p = 0.49
High	9	7.1 %	7	3.5 %	p = 0.15
Income:					
Low	16	11.9 %	15	15.0 %	p = 0.48
Medium	23	6.2 %	27	7.4 %	p = 0.53
High	15	7.1 %	22	5.9 %	p = 0.55
No answer	14	8.9 %	9	11.4 %	p = 0.54
Chronic diseases (of 7 majors):					
None	12	3.9 %	8	3.3 %	p = 0.72
One or more	56	9.9 %	65	9.6 %	p = 0.85
Functional limitations:					
None	46	6.3 %	40	6.0 %	p = 0.79
One or more	22	14.8 %	33	13.1 %	p = 0.64
Cognitive impairment:					
No: MMSE > 23	63	7.4 %	67	7.5 %	p = 0.93
Yes: MMSE ≤ 23	5	19.2 %	6	19.4 %	p = 0.99
Depression:					
No (CESD < 16)	47	6.0 %	42	5.3 %	p = 0.55
Yes (CESD ≥ 16)	21	22.6 %	31	24.0 %	p = 0.80
Anxiety: being fearful					
No	53	6.8 %	49	6.1 %	p = 0.60
Sometimes - often	15	16.9 %	24	20.7 %	p = 0.49
Sleeping problems:					
Never - sometimes	47	6.2 %	36	4.7 %	p = 0.20
Occasionally -often – always	21	17.4 %	37	23.0 %	p = 0.25
Use of alcohol:					
Never	15	11.6 %	12	16.0 %	p = 0.37
Light – moderate	51	7.5 %	56	7.5 %	p = 0.97
(very) excessive	2	3.2 %	5	5.0 %	p = 0.59
Antidepressant use:					
No	62	7.2 %	63	7.1 %	p = 0.96
Yes	6	46.2 %	10	27.8 %	p = 0.23

Table 3 shows the results of the univariate and bivariate logistic regression analyses. We did not find any significant associations between cohort and benzodiazepine use when adjusting for the socio-demographic and health characteristics. In the pooled cohorts, associations with benzodiazepine use were found for female sex, higher education, higher income, chronic physical disease, functional limitations, cognitive impairment, depression, anxiety, sleeping problems and antidepressant use. Benzodiazepine use was lower in respondents with higher alcohol use. The multivariate regression analyses, controlling for all covariates that are associated with benzodiazepine use, showed no statistically significant association between cohort and benzodiazepine use.

Table 3. Odds Ratio with 95% CI for cohort differences in benzodiazepine use controlling for sociodemographic and health measures in LASA-1 and LASA-2, weighed by age and gender.

	Cohort		**Covariate**	
	OR	*95% CI*	*OR*	*95% CI*
Cohort	1.02	0.73-1.44	-	-
Cohort + Female gender:	1.02	0.72-1.44	**2.98**	**2.00-4.41**
Cohort + Older age group:	1.03	0.73-1.45	1.09	0.77-1.54
Cohort + higher education:	1.09	0.77-1.54	**0.44**	**0.25-0.80**
Cohort + higher income:	1.13	0.79-1.60	0.61	0.35-1.05
Cohort + Chronic diseases:	0.95	0.67-1.34	**2.90**	**1.78-4.71**
Cohort + Functional limitations:	0.92	0.65-1.30	**2.45**	**1.70-3.52**
Cohort + Cognitive impairment:	1.02	0.72-1.44	**2.95**	**1.49-5.84**
Cohort + Depression:	0.94	0.66-5.84	**5.12**	**3.51-7.47**
Cohort + Anxiety	0.98	0.62-1.39	**3.43**	**2.29-5.13**

Cohort + Sleeping problems:	0.95	0.66-1.34	**4.47**	**3.11-6.44**
Cohort + use of alcohol:	1.10	0.78-1.56	**0.29**	**0.12-0.69**
Cohort + Antidepressant use:	0.94	0.66-1.33	**6.38**	**3.40-11.98**
Cohort + all significantly associated covariates	0.80	0.54-1.17	-	-

Investigation of interaction between cohort and the independent variables showed a statistically significant interaction for cohort and sleeping problems (OR = 1.90, 90% CI = 1.02-3.55, p = 0.09) and a trend for an interaction for sex (OR = 1.90, 90% CI = 0.97-3.73, p = 0.12). Therefore bivariate analyses were repeated in the separate strata of these covariates (males and females; absence versus presence of sleeping problems). However, no significant associations were found between cohort and benzodiazepine use in these subgroups (results not shown).

Discussion

In the present study shifts in benzodiazepine use from 1992 to 2002 in older people were investigated in a large population-based sample.

In contrast with our expectations, no decrease in benzodiazepine use was found in this period. Factors that are known to be associated with benzodiazepine use such as depression, sleeping problems and antidepressant use did show an increase in the past decade. Also in our study socio-demographic variables, physical health measures and the mental health measures mentioned above showed differences in the two cohorts. Therefore, we found it necessary to take a closer look at the covariates and their association with benzodiazepine use.

The samples were stratified for and weighed by age and gender, resulting in an equal division of males and females and of age in years in both cohorts. Benzodiazepine use in women increased from 10.3% in LASA-1 to 12.2% in LASA-2, whereas in men benzodiazepine use decreased from 5% to 3.2%, but these differences were not statistically significant. No cohort differences in benzodiazepine use were found between the older and the younger age group. Cohort differences in sociodemographic characteristics were found, with a shifting in the levels of education and income towards higher levels. Benzodiazepine use was higher in respondents with low level of income and in the low education group, but there was no

significant difference between the cohorts.

Physical health problems increased from 1992 to 2002. Respondents with one or more chronic diseases used more benzodiazepines in both cohorts, and the same was found for functional limitations. Chronic physical disease and functional limitations may be associated with feelings of distress and sleeping problems. Although benzodiazepines may diminish these problems and improve functional abilities, they can also have an adverse effect, e.g. by causing sedation, muscle weakness and increasing the risk of falling. It is important to pay special attention to benzodiazepine use in this vulnerable group.

The stability in benzodiazepine use in respondents with depression, anxiety complaints, sleeping problems and with antidepressant use in the two cohorts is a remarkable finding. We expected a decrease of benzodiazepine use in these groups as a result of enhanced knowledge and insight in adequate treatment of depression and concomitant or isolated anxiety complaints and sleeping problems, but this was not found. Benzodiazepines may be useful to alleviate symptoms of depression or anxiety disorder such as restlessness, heightened tension, anxiousness and sleeping problems, but it is recommended only for short use or for support in the first weeks of treatment with antidepressants or psychotherapy. Prolonged use of benzodiazepines may even worsen the depressive symptoms (3). Difficulty in sleeping may be an isolated problem, but in that case, only short during support with benzodiazepines is recommended.

The combination of benzodiazepine use and the use of alcohol is important because of the possibility of excessive sedation and mood disturbances. In the alcohol users benzodiazepine use was lower than in the full sample, but there are respondents who combined alcohol with benzodiazepine, which may lead to important health problems e.g. a higher risk of falling, memory problems and traffic accidents.

There are some limitations to this study. The two cohorts with the large amounts of respondents in both cohorts and the wide variety of variables are very well suited for an investigation of trends. However, subgroups using benzodiazepines were small, probably too small to find statistically significant cohort differences. A second limitation of the present study is the use of self-report scales. This may cause report bias, due to problems in the recall of information from the past (chronic disease), or unwillingness or feelings of shame (income, education, alcohol use). However, the main variable in this study, medication use, was recorded directly from the containers.

Conclusion

Overall benzodiazepine use in this older population sample remained stable from 1992 to 2002. A decrease of benzodiazepine use, as was expected based on the increasing insights in the serious consequences of prolonged benzodiazepine use, was not found. Benzodiazepine use in females, and in respondents with low education, low income, chronic physical disease, functional limitations, depression, anxiety complaints, sleeping problems and with antidepressant use remained higher, whereas benzodiazepine use in respondents with alcohol use remained lower. However, it is generally accepted that benzodiazepines are not suited for the longer-lasting treatment of depression, anxiety complaints and sleeping problems. Furthermore, in older people with physical health problems benzodiazepines may lead to worsening of the physical condition and should be prescribed with great care. Benzodiazepine use in combination with alcohol use may lead to excessive sedation. It is necessary that more attention is payed to benzodiazepine use in older people, in order to diminish its negative effects on health and functioning.

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