

A cross-sectional survey on benzodiazepine use among older people in an Italian region

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Abstract

Background. Benzodiazepines are among the most commonly prescribed drugs in Italy and they are often used inappropriately according to guidelines for their rational use.

The aim of this study was to investigate the prevalence and pattern of use of benzodiazepine amongst the general population aged 65-84 years in the Friuli-Venezia Giulia Region, in North-East Italy.

Methods. A total of 40 general practitioners participated in the study. Two data sources were used in the research. The first was the Health Search Database, the second was a short questionnaire administered by the general practitioners to the 65 to 84 year old patients attending their surgeries for any reason during the study period. Data on the use of benzodiazepines between 1st February and 31st July 2001 were extracted from both the Health Search Database using drug prescriptions and the questionnaires.

Results. Of the 10,468 patients aged 65-84 years with complete demographical data in the general practitioners' patient lists, 2,369 subjects used benzodiazepines, hypnotics and over the counter drugs. Overall prevalence of benzodiazepine use was 21.5% (95% confidence interval: 19.8-23.1%). Of the benzodiazepine users, 66.9% consumed a short-intermediate half-life and 33.1% a long half-life benzodiazepine. Most patients took benzodiazepines at night (68.2%), less frequently in the daytime and at night (23.7%), or in the daytime only (8.1%). Most users (89.2%) said they had been taking benzodiazepine for years.

Conclusions. Benzodiazepine use was associated with patient characteristics, such as being female, using analgesics or antidepressants and the presence of a chronic disease especially cancer or chronic heart failure.

Key words: benzodiazepine, cross-sectional study, older people, anxiolytic, hypnotic

Introduction

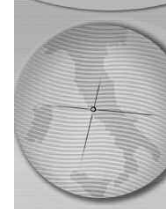
Benzodiazepines are amongst the most commonly prescribed drugs in Western countries, especially among older people, and they are often used inappropriately [1-3] according to current guidelines [4]. This is mainly due to the use of benzodiazepines for the chronic treatment of insomnia, even though prescriptions for such medications should be for short-term use and discontinued afterwards. Furthermore, the prescribing of benzodiazepines may reflect inappropriate diagnosis, since depression may be undiagnosed and therefore under treated using benzodiazepines in primary care.

The aim of this study was to investigate the prevalence and pattern of use of benzodiazepines, and factors related to their use, amongst the general population aged 65 years and over, using two data sources: a computerised general practitioner's (GP) database and an ad-hoc investigation using self-administered questionnaires in the GP's surgery.

Methods

Population

This was a cross-sectional study carried out using a sample of GPs living in the Friuli Venezia Giulia Region, in North-East Italy. The GPs were selected



on a voluntary basis from among the 1,043 working in the region, according to the following criteria: a) geographical area, in order to cover as much of the region as possible; b) previous research experience; c) size of patient population (no less than 700 and preferably more than 1,000).

All subjects aged 65-84 years included in participant GP's database were eligible for the research.

After an information campaign supported by the Regional Health Agency (Agenzia Regionale della Sanità) and the Regional Centre for Medical Training (Centro Regionale di Formazione), 44 GPs were recruited. The selected GPs were also collaborating with the "Health Search" (HS) Institute of Research. The GPs were provided with a personal computer and Millewin software for their routine clinical activity for the Health Search Database (HSD). They also attended a preliminary training course on how to use the software and other tools for the research project. All the GPs' data were stored in the HSD.

The project was approved by the Friuli Venezia Giulia Region's Ethics Committee. All the information on patients and GPs gathered from the HSD and questionnaires were treated anonymously.

Data sources

Two data sources were used in the research. The first was the HSD, a computerised archive which currently contains information from over 550 GPs covering more than 800,000 patients. Data were subject to quality checks in accordance with the procedures followed for other computerised GP databases [5]. GPs who failed to meet standard quality criteria were allowed to improve their performance, although their data were not considered for epidemiological studies. The following data were collected for each patient from the HSD: age, gender and area of residence, presence of some chronic diseases and use of analgesics or antidepressants in the study period.

The second source of data was a short ad-hoc self-administered questionnaire (benzodiazepine questionnaire), which investigated the frequency, quantity and duration of drug consumption by the patient due to "insomnia, nervousness, depression or anxiety".

From 1st February to 31st July 2001, all subjects aged 65-84 years attending their GP's surgery for any reason were invited to fill in the benzodiazepine questionnaire. The two files including data from the HSD and from the self-administered questionnaire for benzodiazepine use were linked using the patient's code.

Although the study focused on benzodiazepines, we also collected information on non-benzodiazepine hypnotics or sedatives. Benzodiazepines were classified according to their half-life and properties as hypnotics or anxiolytics according to common definitions [6].

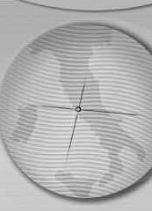
Prevalence of benzodiazepine use was defined as either the patient's positive answer in the benzodiazepines questionnaire or the patient's receipt of a prescription in the HSD in the study period.

Statistical analysis

Prevalence of benzodiazepine use was computed for each GP and for the total sample using the number of current users in the 6-month observation period - as previously defined - as the numerator, and the number of each GP's patients aged 65-84 years with complete demographical data as the denominator. The latter figure was provided by the regional Health Information Service. Prevalence rate estimates and their 95% confidence intervals (95% CIs) were calculated considering the cluster sampling design of the study, each cluster corresponding to the patients of one GP, according to standard methods for population surveys [7]. A total of about 10000 people aged 65-84 years included in participant GP's database were considered as the population base of the study. Based on an expected prevalence for benzodiazepine consumption of about 10%, the study had a precision of 6% in estimating the prevalence of use. The associations between benzodiazepine use and various GP and patient characteristics were evaluated using both univariate and multivariate analyses.

The following patients' characteristics were analyzed for a possible association with the type of benzodiazepine used: age, sex and area of residence. Likewise, some GP's characteristics were also included in the analysis: age, sex, working area (urban area, suburbs, village) and the size of each GP's patient population.

The odd ratios (ORs) and the corresponding 95% CIs were then computed for each factor after adjusting for the possible confounding effect of the others as well as for age and sex, using logistic regression models adjusted for the cluster sampling design. The choice of variables included in the logistic regression model was based on the results of the statistical tests for each variable using univariate analysis. The goodness of fit for the logistic regression models was based on commonly suggested techniques, such as the Hosmer-Lemeshow test [8]. The statistical analyses were performed using the Stata computer

**Table 1. Prevalence rates of benzodiazepine use among all patients and according to their gender and age.**

	No.	% consumers (95% CI) ^a	Total subjects
All subjects	2246	21.5 (19.8-23.1)	10468
Gender	Male	13.7 (12.4-14.9)	4208
	Female	26.7 (24.7-28.7)	6260
Age (years)	65-69	19.5 (17.4-21.7) ^b	2991
	70-74	21.9 (20.0-24.0) ^b	3092
	75-79	22.6 (20.7-24.6) ^b	2887
	80-84	22.0 (19.3-25.0) ^b	1498

^a 95% CI: 95% confidence interval when taking into account the sampling design

^b Chi square for linear trend: $p=0.001$

Percentages are computed on the row total

programme for personal computer (Stata Corp. 2001. Stata Statistical Software: Release 7.0. College Station, TX: Stata Corporation) using two-tailed tests with an alpha level of 0.05 in order to reject the null hypothesis.

Results

Four of the 44 GPs initially enrolled in the project were excluded due to inadequate data registration. The analysis was therefore carried out on data collected by 40 GPs, which covered 10,468 patients aged 65-84 years with complete demographical data from a regional total of 87,544.

The GPs were 41 to 61 years old, only one being over the age of 54, with a mean age of 46.7 years (Standard Deviation, SD: 3.7 years); 77.5% of them were males. The GPs' patient lists included 139-367 (mean: 261.7, SD: 55.9) patients aged 65-84 years, and a total of 743-1,894 (mean: 1,406, SD: 234.2) subjects of all ages. No GPs were specialised in neurology or psychiatry, and 42% of them worked together with other GPs in the same practice.

According to the study design, 1,930 subjects aged 65-84 years received at least one prescription for hypnotics or sedatives in the period as reported in the HSD, and 1,317 subjects filled in the questionnaire claiming to use these drugs. A total of 2,369 subjects who used hypnotics or sedatives were identified through these data sources: 878 of them had both HSD prescription and the questionnaire, 1,052 were found in the HSD file but did not complete the questionnaire, and 439 filled in the questionnaire but were not found in the HSD file. Of the 2,369 subjects who used these drugs, 2,246 (94.7%) used benzodiazepines, 96 other hypnotics, and 27 over-the-counter (OTC) drugs.

A high variability was found in the number of questionnaires collected from each GP, the range being 5-78 (mean 35.5, SD 16.6). Consequently the proportion of old people completing the questionnaire of those assuming benzodiazepines

ranged from 1.7% to 24.6% (mean 14.0%, SD 6.4%). Among GP characteristics, being female, being younger and not working in an urban area were associated positively and independently with the probability of collecting questionnaires from the patients (data not shown in Tables). On the contrary, no patient characteristics, with the exception of their area of residence, were associated with the filling in of a questionnaire; with subjects resident in an urban area providing the lowest number of questionnaires.

Overall, the prevalence of benzodiazepine use was 21.5% (95% CI: 19.8-23.1%), higher in females (26.7%) than in males (13.7%), considering both the HSD and the questionnaire data, with a moderate, statistically significant, linear increase with increasing age up to 75 years and then a plateau (Table 1).

Most subjects claimed to use only one benzodiazepine compound (85.7%). Of the benzodiazepine consumers, 66.9% used a short-intermediate (≤ 24 h half-life) and 33.1% a long (> 24 h) half-life benzodiazepine or both, with no substantial differences by gender.

The most commonly used short-intermediate half-life benzodiazepines were Lorazepam (27.2%) and Bromazepam (17.6%), and the most frequently used half-life benzodiazepine was Chlordemethyldiazepam (18.2%) (Table 2).

Pattern of benzodiazepine use according to half-life is set out in Table 3. As regards time of consumption, most patients, both among short-intermediate and long half-life benzodiazepine consumers, took benzodiazepines at night (68.2%). Most users (89.2%) said they had been taking benzodiazepines for years (chronic users) and we found no differences in the drug's half-life in this respect. The first prescribing physician was the GP in 70.0%, a hospital doctor in 16.2% and a neurologist or psychiatrist in 9.7% of users and no difference were found in first prescribing physicians according to the half-life of benzodiazepines.

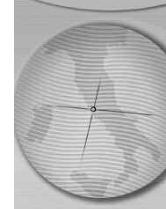


Table 2. Types of benzodiazepine and hypnotic most commonly used according to half-life (subjects consuming more than one benzodiazepine are included in more than one category).

Type	Males (n=575)		Females (n=1671)		Total (n=2246)	
	N	(%)	N	(%)	N	(%)
Benzodiazepines						
Short-intermediate half-life (≤ 24 h)						
Lorazepam	164	(28.5)	449	(26.8)	613	(27.2)
Bromazepam	102	(17.7)	295	(17.6)	397	(17.6)
Alprazolam	62	(10.7)	163	(9.7)	225	(10.0)
Lormetazepam	47	(8.1)	143	(8.5)	190	(8.4)
Triazolam	40	(6.9)	110	(6.5)	150	(6.6)
Etizolam	20	(3.4)	65	(3.8)	85	(3.7)
Brotizolam	13	(2.2)	35	(2.0)	48	(2.1)
Oxazepam	11	(1.9)	32	(1.9)	43	(1.9)
Estazolam	4	(0.7)	26	(1.5)	30	(1.3)
Flunitrazepam	11	(1.9)	13	(0.7)	24	(1.0)
Clotiazepam	3	(0.5)	19	(1.1)	22	(0.9)
Temazepam	1	(0.1)	5	(0.3)	6	(0.2)
Long half-life (>24 h)						
Chlordemethyldiazepam ^a	91	(15.8)	318	(19.0)	409	(18.2)
Diazepam	39	(6.7)	97	(5.8)	136	(6.0)
Flurazepam	26	(4.5)	54	(3.2)	80	(3.5)
Prazepam	19	(3.3)	81	(4.8)	100	(4.4)
Nordiazepam	4	(0.7)	15	(0.9)	19	(0.8)
Nitrazepam	4	(0.7)	10	(0.6)	14	(0.6)
Chlorazepate ^b	3	(0.5)	5	(0.3)	8	(0.3)
Ketazolam ^b	0	(0.0)	5	(0.3)	5	(0.2)
Chlordiazepoxide ^b	2	(0.3)	1	(0.1)	3	(0.1)
Quazepam	0	(0.0)	1	(0.1)	1	(0.1)

^a Delorazepam

^b Although these drugs are short-acting, their metabolites are long-acting benzodiazepines.

Percentages are computed on the column total

Table 3. Pattern of benzodiazepine consumption among the 1252 subjects with questionnaire data on the type of benzodiazepine used.

Pattern of consumption	Type of benzodiazepine					
	Short-intermediate half-life (n=777)		Long half-life (n=475)		All (n=1252)	
	N	(%)	N	(%)	N	(%)
Time of consumption ^{a,b}						
At night	506	(69.7)	292	(65.6)	798	(68.2)
In the daytime	61	(8.4)	34	(7.6)	95	(8.1)
Both	159	(21.9)	119	(26.7)	278	(23.7)
When started use ^b						
Years ago	544	(89.3)	338	(88.9)	882	(89.2)
Months ago	52	(8.5)	36	(9.5)	88	(8.9)
Weeks or days ago	13	(2.1)	6	(1.6)	19	(1.9)
First prescribing physician ^b						
General Practitioner	488	(70.3)	296	(69.7)	784	(70.0)
Neurologist or psychiatrist	72	(10.4)	36	(10.2)	108	(9.7)
Hospital doctor	109	(15.7)	72	(16.9)	181	(16.2)
Others	25	(3.6)	21	(4.9)	46	(4.1)

^a $p < 0.001$

^b Data were not available for all subjects.

Percentages are computed on the column total

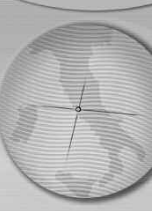


Table 4. Patients' characteristics associated with benzodiazepine consumption using logistic regression models with cluster sampling design: odds ratios for benzodiazepine use and their 95% confidence intervals (95% CI) according to investigated variables

Patients' characteristics	Odds Ratio (95% CI)	p-value*
Gender (Female vs Male)	2.1 (1.9 – 2.3)	< 0.001
Chronic diseases:		
CHD	1.2 (1.0 – 1.5)	0.023
Stroke	1.2 (0.9 – 1.5)	0.056
Cancer	1.3 (1.1 – 1.5)	0.012
Analgesic use	1.9 (1.7 – 2.2)	< 0.001
Antidepressant use	3.7 (3.2 – 4.4)	< 0.001

*Likelihood ratio test

Hosmer-Lemeshow Test: 20.8 (p=0.002)

We classified benzodiazepines according to their properties as hypnotics or anxiolytics as previously written: benzodiazepines classified as anxiolytics were consumed more (75.8%) than the others, with no significant differences for age and sex (data not shown in table). Significant differences were observed in the time of consumption among subjects taking hypnotic or anxiolytic benzodiazepines: 78.8% of the former took them at night only, and 19.9% in the daytime as well; 64.4% of the latter took them at night only and 27.6% in the daytime as well (p<0.001).

The use of two or more benzodiazepines was more common amongst those who consumed hypnotics (21.7%) as compared to those who did not (7.5%) (p<0.001) (data not shown in table).

Using univariate analysis, the presence of chronic diseases, such as stroke, coronary heart disease (CHD) and cancer, and the use of analgesics or antidepressants were significantly associated with benzodiazepine use (p<0.001).

The prevalence of benzodiazepine use when considering individual GPs ranged from 9.9% to 29.4% (mean 21.5%, standard error: 0.8%), showing a normal distribution (Shapiro-Wilks test: p>0.1).

The age, gender and size of each GP's patient population were not associated with differences in the prevalence of benzodiazepine use, whereas area of residence showed a moderate association (p<0.001): benzodiazepines were consumed slightly more often in urban practices (23.5%) than in suburban or village areas (20.0%).

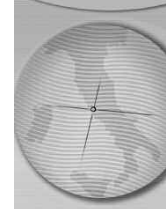
Finally, logistic regression analysis with a cluster sampling design (Table 4) showed that the risk of benzodiazepine use was significantly associated with certain patient characteristics, such as being female (OR=2.1; 95% CI: 1.9-2.3), using analgesics (OR=1.9; 95% CI: 1.7-2.2) or antidepressants (OR=3.7; 95% CI: 3.2-4.4). Also chronic diseases such as presence of cancer (OR=1.3; 95% CI: 1.1-1.5) or coronary heart disease (OR=1.2; 95% CI: 1.0-1.5) were associated with benzodiazepines

use. No GP characteristics were associated with benzodiazepine use when added to the multivariate model (data not shown).

Discussion

One of the aims of this study was to investigate the prevalence of benzodiazepine use amongst older people, using data collected by HSD and a self-administered questionnaire. The validity of the HSD data has recently been evaluated by comparing prevalence estimates for some chronic diseases using the HSD and a national survey based on self reporting, which showed only minor differences between the two sources, for diseases with a clear-cut diagnosis such as diabetes or hypertension [9]. However, the HSD may underestimate the prevalence of use of certain drugs such as benzodiazepines. In fact, 439 of the 2,246 (19.5%) hypnotic or sedative users would have been missed if only the HSD data had been examined, since these patients had not been prescribed these drugs during the 6-month observation period. This is not surprising since benzodiazepines are not reimbursed by the Italian National Health Service, so a patient can obtain a prescription for these drugs from a doctor other than his/her own GP.

About half of the benzodiazepine users (1,052 of the total of 2,246, 46.8%) did not fill in the questionnaire on benzodiazepine use. A high degree of variability in the proportion of questionnaires collected by GPs, taking into consideration the total number of patients taking benzodiazepines, was found (the range was 1.7-24.6%). Various GP characteristics were associated with the number of questionnaires collected, particularly gender, age and area of work, whereas no patient characteristics, apart from area of residence, were associated. This suggests that surveys based on the administration of questionnaires to patients at a general practice may underestimate the true prevalence figures, and are



influenced by the characteristics of the GPs involved in the study. It is noteworthy that previous studies found that benzodiazepine use among older people is often unreported to GPs [10].

Benzodiazepines are still among the most widely prescribed drugs in Western countries [4]. Although a reduction in their use has been observed in some countries during the last few decades [11], in Italy there was a 50% increase from the mid-1980s to the late 1990s [12]. Accordingly, we found a prevalence rate of 22% amongst the eldest category, which was higher for women (26.7%) than men (13.7%). These figures are similar to those observed in studies carried out in the 1990s in Italy [13,14] and in other European countries [15,16].

Short-intermediate half-life benzodiazepines, particularly lorazepam, were consumed more than long-acting ones, which agrees with a recent European study [16]. Benzodiazepines marketed as anxiolytics were used by most subjects (75.8% of users), in accordance with previous observations [14].

Apart from female gender, benzodiazepine use was associated with certain chronic diseases, such as stroke, coronary heart disease and cancer, and with the consumption of anti-depressants or analgesics, in line with other recent studies that found an association between benzodiazepine use and poor general health or the presence of chronic diseases [15,17,18].

Most patients took these drugs at night, probably to help them sleep. This is not in contrast with the findings for more common used benzodiazepines marketed as anxiolytics, since most benzodiazepines act as both anxiolytics and hypnotics. Almost 90% of benzodiazepine users claimed to have been using them for years, and were thus classified as chronic users. Most benzodiazepine users began to take them after a prescription from their GPs, thus confirming the central role of the GP in any health education programme to rationalize the use of these drugs in Italy.

Two possible limitations of this study need to be addressed: the selection of participating GPs and the proportion of patients using benzodiazepines who filled in the questionnaire.

As regards the first issue, we selected the GPs on a volunteer basis, therefore a selection bias cannot be excluded, possibly in the direction of more correct behaviour regarding benzodiazepine prescription according to current guidelines. Should this be true, a low proportion of benzodiazepine users, particularly of chronic users, is expected. On the contrary, we did not find lower prevalence rates for chronic users or

for users of long-acting benzodiazepine compared to those observed in previous studies in Italy [13,14] and other European countries [15,16]. Furthermore, we found no relationship between GP characteristics and the prevalence of benzodiazepine use. Considering these together, the findings do not show a significant bias in estimating the prevalence of benzodiazepine use in this study. Also, other studies have shown that the doctors who contribute to GP research databases do not behave differently than those who do not [5].

Another issue of concern is the use of questionnaire data to describe the pattern of benzodiazepine use among this population, when only 46.8% of the users completed a benzodiazepine questionnaire.

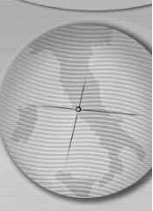
In the 6-month observation period, we expected that almost all of the chronic benzodiazepine users would go to their GPs, at least once, for a prescription for these drugs. Therefore, about half of the older patients who visited their GP for benzodiazepines prescription did not fill in the questionnaire. However, we found no substantial differences between patients who filled in the questionnaire and those who did not with respect to demographic characteristics or the presence of chronic diseases. Therefore, we are confident that the answers given by the patients interviewed can be generalised to all those older people living in North-East Italy.

In conclusion, this study confirms the widespread, mainly chronic, use of benzodiazepine amongst older people, which is associated with female sex and the patient's health status, but not with GP characteristics.

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