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Tolerance to benzodiazepines among long-term users in primary care

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Background. Tolerance towards the effects of benzodiazepines is observed in various animal and human studies. Therefore, it is assumed that patients who use benzodiazepines for a longer period of time need to increase their dose over time to experience the same effect.

Objective. To observe whether long-term benzodiazepine users increase their dose over time.

Methods. From the Dutch National Information Network of Family Practices, a group of long-term benzodiazepine users was identified. This group was divided into an incident long-term benzodiazepine users group ($N = 113$) and a prevalent long-term benzodiazepine users group ($N = 992$). Long-term use of benzodiazepines was defined as usage for at least 6 months. The main outcome was a change in prescribed dose from baseline until 24 months after baseline. Linear regression analysis was performed to evaluate dose change.

Results. Neither incident long-term benzodiazepine users nor prevalent long-term benzodiazepine users were prescribed increasing dosages during follow-up.

Conclusion. There is no increase in prescribed dose among long-term users, as might be expected due to the development of tolerance to the effects of benzodiazepines.

Keywords. Anxiety/anxiety disorder, clinical research, longitudinal, primary care, psychiatry, sleep disorders, substance abuse (not tobacco).

Introduction

Worldwide, benzodiazepines are the most frequently used classes of drugs. In the Netherlands, physicians provide ~11 million prescriptions annually.¹ Primary indications for benzodiazepines are anxiety and insomnia, but they are also used as anticonvulsants, muscle relaxants or pre-anaesthetic sedatives and to reduce symptoms of alcohol withdrawal. Whether a specific benzodiazepine is prescribed for the treatment of sleep or anxiety disorders is largely determined by differences in its pharmacokinetic profile.^{2,3} In anxiety or insomnia, benzodiazepines are the preferred agents only for a short period of time. It is recommended that they should not be used for >4 weeks and only at the lowest dose necessary. Nevertheless, long-term benzodiazepine use is still highly prevalent in Western communities. Depending on the definition for 'long-term benzodiazepine users', the prevalence rates of long-term benzodiazepine use in the general population

vary between 1% (daily use for at least 1 year) and 3% (use for >90 days a year).⁴ Concerning the definitions, most articles refer to 'long-term users' as subjects who have been taking benzodiazepines for at least 1 year,^{5,6} 6 months⁴ or 3 months.^{1,7–9}

Benzodiazepine use has many side effects and the efficacy of long-term treatment has not been established.⁴ Therefore, long-term use of benzodiazepines should be severely restricted. An important issue in long-term benzodiazepine use is dependence and withdrawal. One-third of the long-term (>6 months) benzodiazepine users experience symptoms of withdrawal (e.g. anxiety, insomnia, muscle spasms and tension). Withdrawal symptoms are responsible for continuation of use when subjects interpret them as return of original symptoms. Furthermore, benzodiazepines are widely abused, in the context of recreational and illicit use, with associated risks (due to interactions with other drugs or intravenous use) such as viral infection and local tissue necrosis.¹⁰ Another important issue is the development of tolerance.^{2,5}

'Drug tolerance' is defined as the process by which the effects of the same dose of a drug decrease with repeated administration, resulting in the need to increase the dose to experience the same effect.³ In insomnia, tolerance towards the sedative effect of benzodiazepines has been widely reported in both animals and humans. Time to the development of tolerance towards the sedative effects of benzodiazepines differs between the different types of benzodiazepines. Tolerance develops faster for benzodiazepines with a shorter half-life than for those with longer half-life periods.^{2,3,9,11-13} Tolerance towards the anxiolytic effects has been shown inconsistently in various animal and human studies, and when detected, it appears to occur at a slower rate and to a lesser extent than sedative tolerance.^{2,14-16} There are many receptors known to be involved in the development of tolerance, but the exact mechanisms responsible for it have not been entirely elucidated.^{2,12} The development of tolerance towards the effects of benzodiazepines raises the expectation that long-term benzodiazepine users have to increase their dose over time to experience the same effect. A retrospective study among American long-term benzodiazepine recipients conducted in 2003 showed no increase in benzodiazepine dosages over time.¹⁷ In this study, the prescribed daily dose (PDD) was used to evaluate dose increase, where 10 mg of diazepam was 1 PDD. The incidence of escalation to a higher dosage was 1.6%. However, dosage escalation was defined as a very substantial increase of 2 PDD for elderly or 4 PDD for younger subjects. Subjects using antidepressants or who filled duplicate prescriptions had a higher chance of dosage escalation.¹⁷ The Dutch Health Care system is organized differently than the health care system in the USA. In the Netherlands, >90% of the repeat prescriptions for benzodiazepines are issued by the family physician. Within a registration network of family practices, we were able to investigate whether long-term benzodiazepine users in Dutch primary care increase their dosage over time.

Methods

Study population

The source population consisted of the subjects of the control group of a large benzodiazepine reduction study in family practice (the Benzoredux study, executed from 1998 to 2001).⁷⁸ This natural course control group consisted of long-term benzodiazepine users from 19 family practices, selected from the Dutch National Information Network of Family Practices.¹⁸ Subjects were included in the Benzoredux study if they had been prescribed benzodiazepines for >3 months, with a prescribed amount enough for 60 days of use according to the prescription rules of the family practitioner. During the observation period

of 2.5 years, patients and practitioners in the control group were unaware of their prescription data being observed. Long-term benzodiazepine users who had received prescriptions of benzodiazepines for daily use within the first 6 months of the observation period were selected for the present study. These 6 months were defined as the baseline period for the present study.

The prescription data of benzodiazepines for the 6-month period before the baseline of the current study were used to distinguish two subgroups: the incident long-term benzodiazepine users group and the prevalent long-term benzodiazepine users group. The incident long-term users ($N = 113$) were defined as subjects who did not receive any prescription of benzodiazepines in the 6-month period prior to baseline. After this prescription-free period, this group received prescriptions for benzodiazepines for at least 6 months. These subjects, therefore, were defined as new long-term benzodiazepine users, further called 'incident long-term benzodiazepine users'. In this group, we could observe the pattern of use during the first 2 years of benzodiazepine use. The prevalent long-term users group ($N = 992$) contained subjects who received prescriptions for benzodiazepines in the 6 months prior to baseline and who continued the use of benzodiazepines for at least 6 months after this period. Because they had already used benzodiazepines in the 6-month observation period, they were called prevalent long-term benzodiazepine users.

Measurements and end points

Prescriptions for benzodiazepines [anatomical therapeutic codes (ATC)¹⁹: N05BA, N05CD and N03AE01] were extracted from the family practitioner's electronic medical dossier and converted into diazepam equivalents.²⁰ The number of PDDs was calculated per 3-month period, where 10 mg of diazepam was 1 PDD. We defined the number of PDDs for the first 3-month period after the baseline as the initial dose. The follow-up period consisted of a total of eight 3-month periods. The primary end point was the change in the mean number of PDDs per 3-month period. This was calculated for the incident long-term benzodiazepine users and the prevalent long-term benzodiazepine users.

The secondary end point was the difference in subject characteristics and prescribed benzodiazepine dose changes between patients using normal and those using high benzodiazepine doses in both the incident long-term users and the prevalent long-term users. Patients using high benzodiazepine doses were defined as subjects with a prescription, in the first 3 months after baseline, of ≥ 180 PDDs ($N = 1$ in the incident long-term benzodiazepine users group and $N = 105$ in the prevalent long-term benzodiazepine users group). Patients with a prescription of <180 PDDs in the first

3-month period were considered to be normal-dose users (Figure 1).

This cut-off point of 180 PDDs in a 3-month period, meaning 2 PDDs per day, was chosen for two reasons. First, this clearly marks a higher dose in family practices in the Netherlands, where the majority of benzodiazepine users use an average of ≤ 1 defined daily dose (DDD). Second, in the Benzoredux study, the minimal intervention with a discontinuation letter by the family practitioner appeared to be only effective for subjects using < 2 DDD. A dosage of ≥ 2 PDDs thus indicated a severer dependence profile, with a very low chance of decrease of use in natural course.²¹

The following independent variables were analysed: (i) age (years); (ii) gender (% female); (iii) ATC category: N05BA (anxiolytic) or N05CD (hypnotic), whereby the use of N03AE01 (clonazepam) was included in the anxiolytics group; (iv) type of benzodiazepine used; (v) half-life period of the specific benzodiazepine or its main metabolites (< 24 hours or ≥ 24 hours); (vi) prescription of an antidepressant (measured in the 6- to 9-month period after baseline); and (vii) mean PDDs in each of the subsequent eight 3-month periods of the 2-year follow-up.

Statistical analysis

Statistical comparisons were performed within the total group of benzodiazepine users, as well as in the incident and prevalent long-term benzodiazepine users separately. Patients who were lost to follow-up or who quitted the use of benzodiazepines at

any time in the observation period were excluded from the analysis for the incident long-term benzodiazepine users group ($N = 57$) and for the prevalent long-term benzodiazepine users group ($N = 185$; Fig. 1). Differences in the 3-month mean PDDs were analysed among those who completed the study from within the total group of benzodiazepine users ($N = 863$), the incident long-term benzodiazepine users group ($N = 56$), and the prevalent long-term benzodiazepine users group ($N = 807$; Fig. 1) using linear regression analysis. Differences in subjects' characteristics and prescribed benzodiazepine dose changes between patients using normal and those using high benzodiazepine doses were only calculated for the prevalent long-term users group. In the incident long-term users group, only one patient was defined as a high benzodiazepine dose user and was therefore not entered in the analysis (Fig. 1). Differences in proportions between normal- and high-dose users were analysed with chi-square tests. Analysis of continuous data was performed with Student *t*-tests. A two-sided significance level of 5% was used in all analyses. For the analysis, SPSS package, version 18, was used.²²

Results

Comparisons of study subjects

No clinically significant differences in characteristics between the incident long-term users and the prevalent

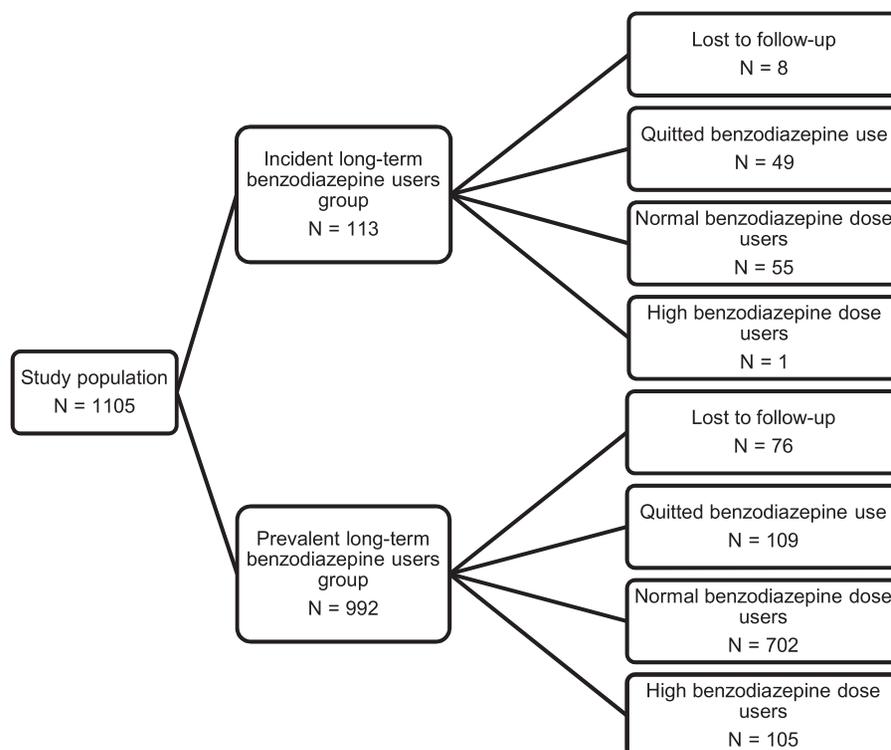


FIGURE 1 Flow diagram of study.

long-term users were observed, except in mean age, which was almost 4 years lower in the incident long-term users (Table 1).

Change in benzodiazepine dose

The mean prescribed dose in PDD per 3-month period in the relevant subgroups are shown in Table 2. Linear regression analyses were performed for the total group of benzodiazepine users, the incident long-term users group and the prevalent long-term users group to establish whether there was an increase in prescribed dose over time in any of the three groups. The regression coefficient (increase in PDD per month) was 0.034 (SEM: 0.148, $P = 0.817$) for the total group of benzodiazepine users and 0.639 (SEM: 0.543, $P = 0.240$) and -0.008 (SEM: 0.153, $P = 0.960$) for the incident long-term users group and the prevalent long-term users group, respectively (Table 3). In addition, linear regression analysis showed no statistically significant increases in prescribed dosages for the subgroups of females only, males only, subjects aged <50 years, 50–75 years, >75 years, anxiolytics users only, hypnotics users only, combination users only and patients who used antidepressants.

Users of normal and high benzodiazepine doses

In Table 4, the characteristics of subjects using normal and high benzodiazepine doses are shown for the prevalent long-term benzodiazepine users group. There is a significant difference in age, whereby high-dose users are younger ($P < 0.01$). Patients using normal doses relatively more frequently used hypnotics (33.3%) compared with patients using high doses (21.0%, $P = 0.01$) and high-dose users more frequently used a combination of benzodiazepines ($P < 0.001$). None of

the high-dose users used temazepam as a single agent ($P < 0.001$). There was a significant difference in antidepressant use. In patients using high doses, 30.5% used antidepressants together with benzodiazepines ($P < 0.001$). In linear regression analysis, no statistically significant increases in prescribed dosages for the subgroups of normal- and high-dose users were observed.

Discussion

In this study, we observed that the prescribed benzodiazepine dosages of long-term users did not increase over time. This was observed in both incident and prevalent long-term users. Furthermore, no increases were observed in the subgroups of anxiolytic or hypnotic benzodiazepine users. Some differences were observed in the comparison of normal- and high-dose users. Users of normal doses were older compared with users of high doses. This may be a reflection of a prescription policy, whereby older subjects are prescribed lower dosages because of a decreased rate of metabolism associated with age. High-dose users more often used a combination of anxiolytics and hypnotics and a greater percentage of the high-dose users used antidepressants compared with the normal-dose users. These findings suggest that users of high doses have severer psychiatric problems. This is in line with the findings of Soumerai, who reported that users of antidepressants had a higher risk of dose escalation.¹⁷

Comparison with the literature

Our study indicated that, although laboratory studies indicated the development of tolerance,¹¹ this aspect had no influence on prescribed benzodiazepine dose in

TABLE 1 Characteristics of study subjects^a

	Total group of benzodiazepine users	Incident long-term benzodiazepine users	Prevalent long-term benzodiazepine users	P-value
N	1105	113	992	–
Age in years, mean (SD)	64.4 (15.7)	61.1 (18.5)	64.9 (15.3)	0.000
Gender (% female)	72.9	66.4	73.7	0.097
ATC				
% Anxiolytics (N05BA)	47.9	51.3	47.5	0.438
% Hypnotics (N05CD)	32.2	31.0	32.4	0.765
% Combination	19.9	17.7	20.2	0.535
Type of benzodiazepine ^b				
% Diazepam	9.0	12.4	8.6	0.205
% Oxazepam	20.9	25.7	20.4	
% Temazepam	18.2	19.5	18.0	
% Other	32.0	24.7	32.8	
Use of antidepressants (%)	18.7	18.6	18.8	0.966

ATC, anatomical therapeutical codes.

^aAssessment was conducted 6 months after baseline.

^bIn users of a single agent, percentages add to 100% with % combination in the table.

TABLE 2 Mean benzodiazepine prescription per 3-month period in terms of PDD

	Total group of benzodiazepine users	Incident long-term benzodiazepine users	Prevalent long-term benzodiazepine users
<i>N</i>	863	56	807
Period			
0–3 months	86.9 (81.5) ^a	50.8 (49.7)	89.4 (82.7)
3–6 months	84.5 (75.6)	62.4 (58.6)	86.0 (76.4)
6–9 months	85.8 (82.2)	63.4 (75.2)	87.3 (82.5)
9–12 months	86.1 (87.5)	64.0 (114.0)	87.6 (85.2)
12–15 months	85.1 (88.8)	66.0 (101.3)	86.4 (87.7)
15–18 months	84.4 (86.0)	58.7 (66.1)	86.2 (86.9)
18–21 months	87.6 (88.1)	66.2 (70.0)	89.1 (89.0)
21–24 months	86.6 (85.8)	72.8 (79.9)	87.6 (86.1)

^aPDD, mean number of prescribed daily dose per 3 months, SD in parentheses.

TABLE 3 Linear regression analyses of benzodiazepine dose change

	Regression coefficient (SEM)	<i>P</i> -value
Total group of benzodiazepine users	0.034 (0.148)	0.817
Incident long-term benzodiazepine users	0.639 (0.543)	0.240
Prevalent long-term benzodiazepine users	–0.008 (0.153)	0.960

TABLE 4 Comparisons between normal-dose users and high-dose users among prevalent long-term users

	Normal-dose users	High-dose users	<i>P</i> -value
<i>N</i>	702	105	–
Age in years, mean (SD)	65.3 (14.7)	60.6 (14.2)	0.009
Gender (% female)	74.5	75.2	0.905
ATC			
% Anxiolytics (N05BA)	48.9	40.0	0.095
% Hypnotics (N05CD)	33.3	21.0	0.013
% Combination	17.8	39.0	0.000
Type of benzodiazepine ^a			
% Diazepam	8.8	8.6	0.000
% Oxazepam	21.8	10.5	
% Temazepam	20.5	0.0	
% Other	31.1	41.9	
Half-life period ^b			
<24 hours	67.9	67.2	0.889
≥24 hours	32.1	32.8	
Use of antidepressants (%)	16.7	30.5	0.001
Mean dose, PDD (SD)			
0–3 months	64.0 (37.5)	258.8 (100.9)	
3–6 months	65.7 (45.2)	221.7 (100.5)	
6–9 months	64.7 (46.7)	239.0 (106.5)	
9–12 months	65.2 (48.4)	237.2 (120.5)	
12–15 months	63.7 (46.2)	238.7 (135.6)	
15–18 months	64.0 (47.6)	235.0 (132.6)	
18–21 months	66.6 (52.4)	239.4 (129.1)	
21–24 months	67.1 (54.7)	224.3 (124.9)	

ATC, anatomical therapeutical codes.

^aIn users of a single agent, percentages add to 100% with % combination in the table.

^bData of users of a single benzodiazepine only.

long-term users in clinical practice.^{2,3,9,11–16} These findings are in line with the results of a study in the USA, where no changes in dosage were observed over time

in a large cohort of benzodiazepine users.¹⁷ However, we cannot answer the question whether our data indicate that subjects do not ask for dose increases or

whether they reflect the result of a policy of GPs who stand firm and do not acknowledge a request for dose increases by patients. Some authors hypothesize that patients continue to take benzodiazepines mainly to compensate for the withdrawal effects and that there is a strong placebo component involved in continued use.⁶ On the other hand, the development of tolerance differs for the various effects of benzodiazepines. It has been suggested that subjects develop complete tolerance for sedative–hypnotic effects but only partial tolerance for anxiolytic effects.^{16,17} Therefore, continued use can also be explained by anxiolytic effects. Observational data of the natural course of long-term benzodiazepine use until now were scarce and not conclusive. Furthermore, various definitions of long-term benzodiazepine use make comparisons between studies difficult.^{6,17}

Strengths and limitations

The strength of this study is that we observed a large group of subjects, with a clear definition of long-term use and with a sufficient duration of follow-up that was adequately monitored by the family practitioner by 3-month measurements of the prescription data. There are some limitations to this study. First, we measured the prescription of benzodiazepines by the family practitioners and not the actual intake. Patients may have received benzodiazepines from sources other than their family practitioner. However, in the Netherlands, >90% of the benzodiazepine prescriptions are prescribed by family practitioners. The remaining 10% is prescribed by specialists, mainly psychiatrists in hospitals or other institutions. Subjects who solely received prescriptions of benzodiazepines by specialists, however, were not included in the original family-practice-based study (the Benzoredux study). Moreover, in the Dutch health care system, subjects are linked to only one family practitioner and to one pharmacy. Prescriptions can be filled at other pharmacies, but the basic pharmacy of the patient is informed and will register the prescription.^{7,8} In many countries, there is a street and Internet market for benzodiazepines. This involves selling of prescribed benzodiazepines, without their taking by the subject who received the prescription, or buying of pills on the street or over the Internet. Data that describe the scale of the street market for benzodiazepines in the Netherlands are lacking. As patients included in our study have a long-term treatment relationship with their family physician, we consider the invalidation of our measurements by possible unknown trading of benzodiazepines by study subjects to be minor. A blood test or urine analysis could have provided us with a more valid intake registration. However, because we used the data of a former study, we were not able to perform these measurements. A second remark can be made concerning the incident long-term benzodiazepine users. We knew from the prescription data that they did

not receive any prescription for benzodiazepines for 6 months, so we considered them to be benzodiazepine starters. These subjects, however, may have used benzodiazepines in the time preceding this 6-month prescription-free period. Due to the pharmacokinetic effects of benzodiazepines, however, earlier intake will not have invalidated our data. Another remark can be made on the validity of the PDD measurement in the first 3-month period in the incident long-term users group. The mean number of PDDs is 19% lower in this period compared with the second 3-month period. Because subjects received the first prescription at some time in this period, the cumulative dose (in PDD) calculated for these 3 months will be lower due to less days of use in this 3-month period compared with the following 3-month periods. A final remark concerns the validity of the data in time. The data used in this study were collected about 10 years earlier. However, the effect of the development of tolerance is not related to the time period when the observation took place. The drugs used 10 years ago do not differ from the main agents still prescribed at present.

Conclusion

Our hypothesis was that due to the development of tolerance, patients need to increase their benzodiazepine dose over time. This study showed that a possible development of tolerance does not lead to increased benzodiazepine prescription over time in daily practice in the Netherlands.

Declaration

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Ethical approval: none.

Conflict of interest: none.

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