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Different study criteria affect the prevalence of benzodiazepine use

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Abstract *Background* Different prevalences of benzodiazepine (BZ) use are described in the literature. The present study assessed the effects of employing various definitions of BZ use and various observation periods on the prevalence rate of BZ use in an open population aged 18–74 years. *Method* In a literature review, prevalence studies were systematically compared. In a second stage, a descriptive cross-sectional multipractice study was analysed using 48,046 prescriptions of BZ in the past year given to a population of 80,315 patients at 31 general practices in the Nijmegen Health Area. From this database, prevalence rates were calculated applying different definitions of BZ use and different observation periods. *Results* In the literature, prevalence rates varied between 2.2 and 17.6 %. There was wide variation in definitions of BZ use and observation period. In our prescription database, depending on the definitions of BZ use and observation period, prevalence rates ranged from 0.2 % to 8.9 %. The ratio of female:male (2:1) remained constant irrespective of the prevalence rate. Age distribution varied according to the duration of use: among long-term BZ users, approximately 80 % were older than 45 years; among short-term BZ users, approximately 55 % were older than 45 years. *Conclusions* The wide variation in prevalence rates of BZ use reported in the literature can largely be explained by differences in definitions of BZ use and observation period. This affected the distribution of some BZ-use-related variables such as age. For reliable comparisons of BZ use, standardisation of the definition of BZ use is required. A proposal for standardising methodology is presented.

Key words Benzodiazepine – Prevalence – Short-term benzodiazepine use – Long-term benzodiazepine use – General practice – Epidemiology

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Introduction

Negative health effects (cognitive deterioration, dependence, falls and fractures) accompany long-term benzodiazepine use, but beneficial effects of long-term use have not been established [1–14]. Medical authorities in many countries, therefore, advise limiting benzodiazepine (BZ) prescription to a small number of time-restricted indications (acute insomnia, acute anxiety and alcohol detoxification) [15–17]. Nevertheless, actual medical practice continues to deviate from these recommendations and BZs are one of the most frequently prescribed classes of drug [18, 19].

As the high prevalence of BZ use is a matter of great concern [20], many studies have been performed on the prevalence of BZ prescription and its use [15, 18, 21–27]. These studies reported a wide range of prevalence rates (for a review see [28]) which does little to clarify the situation.

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Various authors analysed populations that differed in terms of sex, age, social class and years of the study, which resulted in "real" differences in BZ prevalence. The studies also differed in their definitions of BZ use (long-term/short-term/ever), in the methods used to collect data (interview [18, 22, 29] or searching prescription records [30]) and in the study period over which they actually measured BZ use. This may have resulted in "artificial" differences in BZ prevalence and, therefore, hampers the monitoring of trends in BZ use.

The aim of this study was to investigate artificial differences by focusing on two of their main sources: differences in the definition of BZ use and differences in the study period in which BZ use was measured, further referred to as "observation period". A literature study was performed to demonstrate that there is wide variation in the operationalisation of these two aspects and that this leads to the reporting of different prevalence rates. Subsequently, the effects of different definitions of BZ use and different observation periods were assessed using population-based BZ prescription data. We also investigated the effects of different definitions on sex ratio and age. Based on the results of these analyses, recommendations are made about standardising study criteria.

Subjects and methods

First, a systematic literature review was performed on the definition of BZ use and study methods. Secondly, the effects of employing different definitions of BZ use and observation periods were investigated in a primary care population of BZ users.

Literature review

The aim of the review was to analyse BZ use in open populations in relation to the definition of use and observation period. We used Medline and Psyclit to search the literature from 1966 to 2000 with the following entries: "benzodiazepine(s)" accompanied by one or two of the following entries: "prevalence", "epidemiology", "general practice", "family medicine", "population characteristics", "population survey". Also the reference lists of the reports were searched for complementary publications. We included population surveys and studies in primary care/general practice in which the frequency of BZ use and observation period as well as the method of assessing and reporting prevalence rates were explicitly stated. Studies that were ambiguous in this respect (for example "regular" or "occasional" use) were excluded [31–36]. The emphasis was on highlighting the diversity of definitions of BZ use, rather than on compiling a complete list of definitions. Definitions of BZ use and prevalence rates were noted from these publications.

Observational study at 31 general practices

The study was the first step in a computerised intervention programme to reduce inappropriate use of psychotropic drugs and to measure prevalences of psychopathology in the open population [18, 37]. The setting was 31 general practices in the Nijmegen Health Area (NHA). The NHA population comprised non-institutionalised adults from 18 to 75 years of age (total N = ±326,000, Nijmegen N = ±113,000). Health care in the Netherlands is primary-care based; general practitioners (GP) are the gateway to specialised medical care. Specialist care is obtained through referral and the specialists have to report back to the GP. In addition, patients have to register with a GP to receive medical care [38]. General practice records, therefore, provide an overview of all medical care that a patient receives. In this way, the general practice population is virtually identical to the open population.

At present in the Netherlands, approximately 80 % of general practices have computerised patient registration systems and the percentage is rapidly increasing. To participate in this study the computerised general practice registration system had to have been in operation for at least 1 year and the GP had to have been working at the practice for at least 2 years.

We approached 64 practices that fulfilled these criteria and were evenly spread over the region. The objective was to recruit a minimum of 30 general practices in the NHA. Thirty-two general practices agreed to participate in the study. The reasons for non-participation were: involvement in other research projects during the study period (21), refusal to be involved in research (5), on holiday (5), no reason (1). One practice encountered major problems with its computer during the study period and had to withdraw. Therefore, data were available from 31 general practices. The registered patient population was 108,960 persons; this covered a third of the NHA population. The study population aged 18–75 years comprised 80,315 subjects. Compared to the Dutch population, the age group 25–44 years was overrepresented and the age group 45–74 years was underrepresented. Sex distribution was the same as in the Dutch population. The participating general practices did not differ significantly from the non-participants with regard to practice size, number of GPs working at the practice, total length of employment of the GP, dispensing practices, sex and year of registration. The only significant difference was the higher number of GP training centres among the participating general practices ($\chi^2 = 5.6$, $p = 0.02$). In this way a representative sample of general practices was recruited.

BZ prescription data registered between June/July 1996 and May/June 1997 at the participating general practices were made anonymous and converted into a prescription-database.

Under the Dutch health insurance guidelines BZs (no OTC) can only be prescribed by a medical practitioner and a single prescription of BZ cannot exceed a maximum of 30 days. A total of 48,046 BZ prescriptions were converted into prescription records. BZ medication included the ATC-coded groups N05BA, CD, CF and CG. Anxiolytics included N05BA and hypnotics included N05CD, CF and CG. Each prescription record contained the following information: 1) a unique patient identification number, birth date, sex, part of the post code, type of health insurance; 2) date of prescription; 3) the Anatomical Therapeutic Chemical classification (ATC code) [39] of the drug; 4) the total amount of drug prescribed; 5) dosage and frequency per day. This information was used to construct a medication prescription database, in which every prescription for every registered patient was translated into the use/non-use for each day of the whole observation year. When daily use was not specified, we applied the following standard procedure: the prescription records were searched for an earlier prescription, which was more specific. If this was available, the dosage and frequency were used. If not, we looked for a pattern in the prescriptions that reflected a consumption pattern (e. g. 30 tablets every month is consistent with a consumption pattern of one tablet a day). If none of this information was available, we used the advised daily dose of the WHO [39] (DDD), with the exception of oxazepam for which we took 30 mg/day.

With the aid of this prescription database, BZ use was calculated using the following definitions of use from the literature that could be reproduced in our database: 1) (over)all BZ use in a year; 2) short-term use, 2a) BZ use for a maximum of 30 days in a year, 2b) BZ use for a maximum of 90 days in a year; 3) long-term use, 3a) a minimum of 91 days of BZ use in a year, 3b) a minimum of 180 days of BZ use in a year, 3c) a full year of BZ use (as a proxy we took a minimum of 330 days of BZ use). We combined all the definitions of BZ use with different observation periods, namely a year, 3 months, 1 month or 1 day. This combination resulted in prevalence rates for a year, 3 months, 1 month and 1 day. Results were calculated over all benzodiazepines as well as over anxiolytics and hypnotics as separate groups. Anxiolytics and hypnotics were defined according to the ATC codes.

With the SAS-package, prevalence rates were calculated from this database while applying different definitions of BZ use and different observation periods.

Results

The definitions of BZ use and the observation periods in the literature are described in two tables. Table 1 illustrates the effect of employing different observation periods on the definition of overall BZ use. Overall BZ use was usually defined as "at least once" or "at least one tablet or prescription". Column 2 shows the different observation periods, which ranged from 1 year to 1 day. These combinations resulted in prevalence rates that ranged from 17.6 % [22] to 2.2 % [40]. Table 2 illustrates the effect of employing different definitions of long-term BZ use (e. g. longer than 6 months or 12 months, or counting the repeat prescriptions in a given period). Many different observation periods were applied to one BZ use definition (column 2). The prevalence rates did not show any systematic relation with the various BZ use definitions or the different observation periods.

In the second part of the study we investigated the effects of employing different definitions of BZ use and different observation periods in our prescription database (Table 3). In 1 year, nearly 9 % (8.9 %) of the patients received at least one prescription of BZ. The percentage of long-term users varied with the definition. With the most restrictive duration of 1 year of use, 0.6 % were classified as "long-term users"; with more than 180 days of use, 2 % were classified as "long-term users"; and with more than 90 days of use, 2.9 % were classified as "long-term users". Likewise, the percentage of short-term users was lowest when the more restrictive definition of BZ use was employed (3.4 % with ≤ 30 days) and highest

Table 1 Consequences of different definitions of BZ use

BZ use	Observation period	Prevalence % ± 95 C. I. range	Comments	NHA prevalence
BZ use during the observation period with a minimum of one tablet or one prescription	1 year	11.0 (9.9–12.2) [18]	A H	6.6*
		7.4 (6.1–8.9) [22] – 17.6 (15.9–19.4) [22]	A C	6.6*
		12.1 (11.6–12.7) [47, 55]–10.0 (9.5–10.5) [47, 55]	F	8.9
		6.2 (5.9–6.5) [56]	I	8.9
	6 months	3.8 (3.7–3.9) [30]	K	–
	3 months	6.9 (6.7–7.1) [54]	B	5.2
	1 week	8.6 (7.6–9.7) [27]	B	–
	3 days	14.0 (12.5–15.7) [32]	J	–
	1 day	3.0 (2.7–3.4) [26]		2.5
		2.2 (1.8–2.6) [40]	E	2.5

A = only anxiolytics
B = rates derived from general practice computerised prescription data
C = multinational study, only lowest and highest rates are listed
D = exclusion was: "only used as sleeping tablet"
E = survey, telephone interview
F = pharmacy records from population of one village in 1983 and 1992
G = repeat prescriptions
H = anxiolytics comprising 84 % BZ + 16 % barbiturates
I = pharmacy records adjusted for national estimates
J = patients who visited the general practice in the observation period
K = pharmacy record health maintenance organisation
* only anxiolytics

Table 2 Consequences of different definitions of long-term or chronic BZ-use

Definition long-term BZ use		Observation period	Prevalence % ± 95 C. I. range	Comments
12 months (or more)		1 year	1.7 (1.2–2.2) [18]	A H
			1.7 (1.1–2.5) [22]–5.8 (4.8–6.9) [22]	A C
		3 months	1.6 (1.3–2.0) [24]	B D
			1.6 (1.2–2.1) [42]	B
		6 weeks	3.5 (3.4–3.7) [28, 46]	B
		3 days	4.7 (3.8–5.8) [32]	J
		1 day	0.5 (0.4-0.6) [48]	B
			0.9 (0.7–1.3)^{hypnotics} [40]–0.4 (0.3–0.7)^{anxiolytics} [40]	E
More than 6 months in a year		1 year	3.8 (3.5–4.1) [47, 55]	F
			3.1 (2.8–3.4) [47, 55]	
		1 week	4.9 (4.2–5.8) [27]	B
More than 60 days in 6 months		6 months	1.0 (1.0–1.1) [30]	K
Prescriptions	Prescriptions for ≥ 1 year	1 year	2.2 (1.8–2.7) [43]	B G
	≥ three prescriptions	3 months	2.6 (2.4–2.9) [44]	B G

A = only anxiolytics
B = rates derived from general practice computerised prescription data
C = multinational study, only lowest and highest rates are listed
D = exclusion was: "only used as sleeping tablet"
E = survey, telephone interview
F = pharmacy records from population of one village in 1983 and 1992
G = repeat prescriptions
H = anxiolytics comprising 84 % BZ + 16 % barbiturates
I = pharmacy records adjusted for national estimates
J = patients who visited the general practice in the observation period
K = pharmacy record health maintenance organisation
* only anxiolytics

Table 3 Effects of varying the definitions of BZ use and observation period on prevalence rates of benzodiazepine use

	1 year observation	3 months observation	1 month observation	1 day observation
All use				
1–365 days	8.9%*	5.2%	3.7%	2.5%
Short-term use definitions				
≤30 days	3.4%**	1.4%	0.6%	0.2%
≤90 days	4.0%**	1.9%	0.9%	0.4%
Long-term use definitions				
> 90 days	2.9%	2.8%	2.5%	2.0%
≥180 days	2.0%	2.0%	2.0%	1.7%
1 year	0.6%	0.6%	0.6%	0.6%

* Prevalence corrected for the age-sex distribution of the Dutch population: 9.5%
** Missing data due to overlap observation period

Table 4 Proportion (%) of female cases in the prevalence rates of BZ use

	1 year observation	3 months observation	1 month observation	1 day observation
All use % female				
1–365 days	63.9	65.5	65.4	65.2
Short-term use definitions % female				
≤30 days	61.3	62.0	61.6	62.7
≤90 days	62.3	64.1	64.1	64.3
Long-term use definitions % female				
> 90 days	65.2	65.3	65.0	65.1
≥180 days	64.3	64.3	64.2	64.0
1 year	65.3	65.6	65.3	64.9

Table 5 Proportion (%) of people aged > 45 years in prevalence rates of BZ use

	1 year observation	3 months observation	1 month observation	1 day observation
All use definitions % > 45 years				
1–365 days	62.6	69.7	73.7	76.1
Short-term use definitions % > 45 years				
≤30 days	51.1	51.5	51.3	55.9
≤90 days	53.8	56.4	57.9	62.2
Long-term use definitions % > 45 years				
> 90 days	79.0	79.4	79.6	78.7
≥180 days	80.7	80.7	80.6	80.2
1 year	81.7	81.7	81.7	81.6

when the less restrictive definition was employed (4% with ≤ 90 days).

The observation period also affected the prevalence of BZ use: the longer the observation period, the higher the prevalence. With a observation period of 1 day, 2.5% were classified as (all types of) BZ user; with 1 month, 3.7% were users; with 3 months, 5.2% were users; and with 1 year, 8.9% were users. The effect of varying the observation period interacted with the type of BZ use (short-term or long-term) and proved to be more powerful for short-term than for long-term BZ use. For long-term use (defined as a full year of BZ use) the different observation periods had virtually no effect. For short-term use, the prevalence rate for ≤ 30 days varied from 0.2% with a 1-day observation period to 3.4% with a 1-year observation period.

Different definitions of BZ use and different observation periods also affected the prevalence rates of anxiolytics and hypnotics. When, for example, we varied the definition of BZs but employed a fixed observation period (of 1 year), Table 3 column 1 showed that the prevalence rate for that BZ use definition was 8.9%; for BZ use of ≤ 90 days, it was 4%; for BZ use of ≥ 180 days, it was 2%; and for the remaining definition, it was 2.9%. For anxiolytics only, these percentages were 5.3%, 1%, 2.6% and 1.7%, respectively. For hypnotics only, these percentages were 2.3%, 0.5%, 1.2% and 0.7%, respectively. Missing values were caused by users of anxiolytics and hypnotics combined. Note that the rate of anxiolytics by hypnotics for this year prevalence was about 2:1.

We investigated what the consequences were on the sex/age characteristics of BZ users. In each of the calculated BZ use prevalences, 61.3–65.5% were female; among the non-users, 49.5% were female (Dutch population 49.9%). Irrespective of how the prevalence was generated, the ratio of female users to male users remained fairly constant 2:1 (see Table 4). Table 5 illustrates that employing different definitions and observation periods caused the distribution of age to fluctuate. In the short-term users (≤ 30 days/year), 51.1% were older than 45 years (45+); in the long-term users (year/year), 81.7% were 45+ (Dutch population 42.1%). The proportion of 45+ was fairly constant in the long-term users. In the short-term users, the longer the observation period, the lower the proportion of over 45-year-olds (≤ 90 days/day 62.2% were 45+; ≤ 90 days/year 53.8% were 45+).

Discussion

This study focused on two methodology-related issues that affected BZ prevalence rates, namely the definition of BZ use and observation period. In the literature, two major sources of variation in BZ use are mentioned, real (e. g. country) and artificial (e. g. definition of BZ use). We did not find any systematic pattern in prevalence rates in relation to the definition of BZ use or the observation period. This lack of a pattern might be the result of other differences between studies, such as the inclusion or exclusion of drugs labelled as "BZ", method of data collection, country, study year and population composition [41].

We compiled a prescription database, comparable with those described in the literature, to investigate the effect of varying the definition of BZ use and the observation period. The longer the observation period, the higher the prevalence, owing to the inclusion of short-term users."Long-term" users, on the other hand, were always included irrespective of the length of the observation period. Varying the observation period had little

effect on the male:female ratio, but resulted in substantial differences in age distribution. The longer the observation period, the lower the proportion of older BZ users, because of the inclusion of more short-term BZ users. Our results on long-term BZ users were comparable with those reported in the literature with respect to their being older (45+ years). Broadly speaking, our results regarding BZ use also applied to anxiolytics and hypnotics.

Methodology-related aspects

Part of this study comprised an analysis of prescription records from general practice. In the literature registered prescription data are a widely accepted source of data [24, 27, 28, 42–49]. For example, Wright described a point prevalence of 0.5 % for long-term daytime BZ use (> 1 year) in the UK, while we found 0.6 % for day- and night-time BZ use several years later [28]. Patients who received a prescription for BZs were regarded to be BZ users, but it is impossible to say whether the prescription resulted in actual BZ use. Therefore, BZ use may have been over estimated. Although *prescription* does not necessarily imply *use*, it can be expected that the effects of different definitions on prescription rates also apply to user rates. A flaw in our design of short-term BZ use was that we had not foreseen the problem that prescription periods overlapped the beginning and the end of the 1-year collection period. To obtain the BZ use characteristics for all patients for a full year, it would be better to extend the observation period slightly, for example to 14 months, to make it easier to classify the BZ users who overlap the beginning or end of the observation period. Some studies count prescriptions, but this method is less accurate than the method we applied, because medication can be prescribed for a few days to 1 month (e. g. psychofarmaca) or even several months (e. g. other medication). Some other studies used interviews as a method of data collection [18, 22, 23, 26, 29, 40, 50], which may have produced more reliable information about actual BZ use. A disadvantage of interviews is bias caused by (selective) recall or by leading questions, or random bias caused by the response set. Janson remarked "the evidence is overwhelming that recollecting tends to decrease with the time span involved" [51–53]. The method of data collection is one of the sources of artificial differences in prevalence; other sources are the research design (cross-sectional or longitudinal) and the research sample (age range, age composition and sex composition).

Although the variation in reported BZ use is the consequence of a number of factors, our framework of varying BZ use definitions and observation periods resulted in fairly consistent results. Compared to other studies in the Netherlands, for instance in Van Hulten's study [47] long-term BZ use (more than 6 months BZ use in a 1-year observation period) prevalence was 3.1 % in 1992, while ours was 2 % in 1997. The overall prevalence in Van Hulten's study was 10 %, while, after being corrected for the age-sex distribution of the Dutch population, ours was 9.5 %. Our results were also consistent with the overall prevalence in the study by Van de Waals [54] reported in 1987. A 3-month observation period led to a prevalence of 6.9 % compared to our prevalence of 5.2 %. Controlling for methodology variation would make it possible to uncover relevant differences in BZ use between countries and cultures [22] and this could provide a starting point for more in-depth analysis of the reasons behind the gap between desired and observed BZ use.

Uniformity of criteria and observation periods is vital. This study emphasises the need to standardise the criteria for investigating BZ use in order to be able to make meaningful comparisons. On the basis of our Dutch population, we developed a framework for converting reported prevalence rates by taking into account differences in two important variables that cause artificial differences. It may be possible to develop a universal conversion method that is suitable for making comparisons between various studies. However, from our experience this seems to be a cumbersome approach. An alternative would be to reach international consensus about study procedures. Firstly, we propose employing an observation period of 1-year, because this is the standard measure of prevalence. Secondly, there should be only 3 (reference) definitions of BZ use (anxiolytics and hypnotics together): (1) any use in the past year (ever); (2) short-term use in the past year with a maximum of 3 months (the advice of the WHO); and (3) long-term BZ use in the past year when 6 months of BZ use has been exceeded.

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