Drug utilization review of oral forms of benzodiazepines in a Belgian 635-bed teaching hospital

● N. Petit, J.-P. Delporte, M. Ansseau, A. Albert and F. Jeusette

Introduction

Comparative studies have shown that Belgium [1], in particular the Liège area [2], is one of the countries with the highest rate of benzodiazepine consumption. High rates of benzodiazepine prescription and utilization in hospitals, and the influence of sex and age were previously reported [3-6]. The potential role of hospitalization in initiating benzodiazepine consumption after discharge was also previously discussed [7-9].

The present study was designed to establish a chart of the consumption of benzodiazepines administered orally in a 635-bed teaching hospital, in Liège, Belgium. Other objectives were to determine the influence of patient-related parameters like sex and age, and of hospital-related parameters (type of services, ward prescription habits, etc.) on benzodiazepine utilization, and finally to assess to which extent benzodiazepine consumption habits can be induced by hospitalization. The study was mainly oriented towards the utilization of benzodiazepines administered orally because we wanted to focus more on the 'conscious' intake of benzodiazepine, as observed in most clinical situations, than on the 'unconscious' intake when they are parenterally administered during technical acts (surgery, endoscopy, interventional radiology, etc.) or, at a transitory step, in intensive care units (ICU). However, in order to assess an overall consumption of benzodiazepines in this hospital, a rough estimation of parenteral utilization is also given.

Methods

The study received prior approval from the Ethics Committee of the University Hospital in accordance with the 1983 Helsinki Declaration. Patient-related data (age, sex, ward, length of stay) and benzodiazepine consumption-related data (type of medication, dosage, regimen, length and profile of treatment) were collected from 4,307 patient drug records (nearly 20% of yearly in-patient records) during four periods in 1991 (February, May, August and November). All consecutive record forms for all patients included in the study were surveyed from the admission to the discharge. Data were collected using software developed by the pharmacy department. Data were analysed using Student's t-test, chi square test and analysis of variance. A value of p <0.05 was considered to be statistically significant.

The proportion of patients exposed to benzodiazepines before admission was evaluated from medication profiles and medical records, assuming that a patient who used benzodiazepines before admission, would be provided with a benzodiazepine prescription at the beginning of the hospitalization. A random sample of fifty medical records of patients having received a benzodiazepine prescription on the first day of the stay were selected and medi-

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Abstract
A retrospective study based on 4,307 drug patient records was designed to establish a chart of the consumption of benzodiazepines administered orally in a 635-bed teaching hospital, and to determine the influence of patient-related parameters (age, sex) and hospital-related parameters (type of services, prescription habits, etc.) on benzodiazepine utilization. Another objective was to evaluate to which extent benzodiazepine consumption can be induced by hospitalization. A minor but statistically significant difference (p <0.05) was observed between the proportion of male (42.7%) and female (46.5%) users. Besides, when evaluating the consumption in number of defined daily doses per 100 beddays, there was little difference between the consumption of male (51.2 defined daily doses per 100 beddays) and female (52.8 defined daily doses per 100 beddays) patients. A significant influence of age was also observed with an increase of benzodiazepine use for patients aged from 15-20 to 40-45, followed by a progressive decrease for higher ages. With hypnotics, no peak of consumption related to age was observed but an increase of consumption from age 15-20 to 30-35. For higher ages the consumption of hypnotics was nearly stable or rising slowly. High variations in benzodiazepine utilization were recorded between hospital wards (median: 50.77 defined daily doses per 100 beddays, range 0.23-263.9). Finally, it was found that 6.8% of patients with a benzodiazepine treatment initiated during hospitalization may be considered as potential benzodiazepine consumers after discharge.

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Table 1 *Population and benzodiazepine prescription data during the study periods based on 4,307 patient records*

Ward	Number of patients*			Number of beddays			Mean length of stay (days)		Patients with benzodiazepine prescription (%)			Mean length of benzodia-zepine treat-ment (days)	
	M	F	M+F	M	F	M+F	M	F	M	F	M+F	M	F
Medicine	932	751	1,683	9,769	8,715	18,484	10.5	11.6	43.8	47.0	45.2	8.1	9.2
Surgery	783	573	1,356	8,018	5,627	13,645	9.8	10.1	55.6	61.4	58.0	4.6	5.0
Mixed	406	284	690	2,306	1,791	4,097	5.7	6.3	16.0	19.7	17.4	3.3	3.0
Intensive care	311	164	475	1,903	1,319	3,222	6.1	8.0	43.4	43.9	43.6	4.2	5.8
Unknown	50	53	103	276	261	537	5.5	4.9	34.0	30.2	32.0	3.1	3.6
Total	2,482	1,825	4,307	22,272	17,713	39,985	9.0	9.7	42.7	46.5	44.3	–	–

*F: female; M: male.

cations before admission surveyed, in order to roughly estimate the proportion of patients who were benzodiazepine users before admission.

In the same way, induced benzodiazepine consumption after discharge was evaluated from medication profiles and medical records, assuming that a patient who used no benzodiazepines when admitted to the hospital but was discharged with a benzodiazepine prescription, is a potential medium- or long-term consumer. To verify this assumption, a random sample of fifty medical records of patients, non-users at admission but initiated to benzodiazepine usage during the stay up to its end, was surveyed and medications at discharge examined.

Benzodiazepine utilization was evaluated according to anatomical-therapeutical-chemical (ATC) class, distinguishing hypnotics (N05CD) and anxiolytics (N05BA) [10]. The consumption was expressed in defined daily doses (DDD), in DDD per 100 beddays and in number of prescriptions. DDDs of the most used benzodiazepines were compared with calculated mean prescribed daily doses (PDD), determined from drug patient records.

Results

Population data

During the four study periods, 4,307 patient records were examined. 2.3% of these records could not be identified with respect to the ward where the patient had been admitted. The mean age of the patients was 50.2 years. The age distribution was non-gaussian and the median value was 56.0 years. There was no significant difference between the four periods. The overall mean ratio of male to female in-patients was 58/42 and no significant differences were found between the periods, except in August with a ratio of 62/38. The ratio of patients admitted to the various wards (internal medicine, surgery, mixed internal medicine/surgery, and intensive care) was the same during the four periods (p >0.05] (Table 1). Since no significant differences were observed between the population parameters of the four study periods, most data were combined into a single sample. The average hospital stay was 9.3 days, ranging from 5.9 days in mixed wards to 11.0 days in internal medicine wards (p <0.05).

Influence of patient sex on benzodiazepine prescription

Regardless of the study periods and wards, there was a small but significant difference between the proportions of male (42.7%) and female (46.5%) benzodiazepine consumers (Table 2). However, when restricting prescription analysis to hypnotics (N05CD,
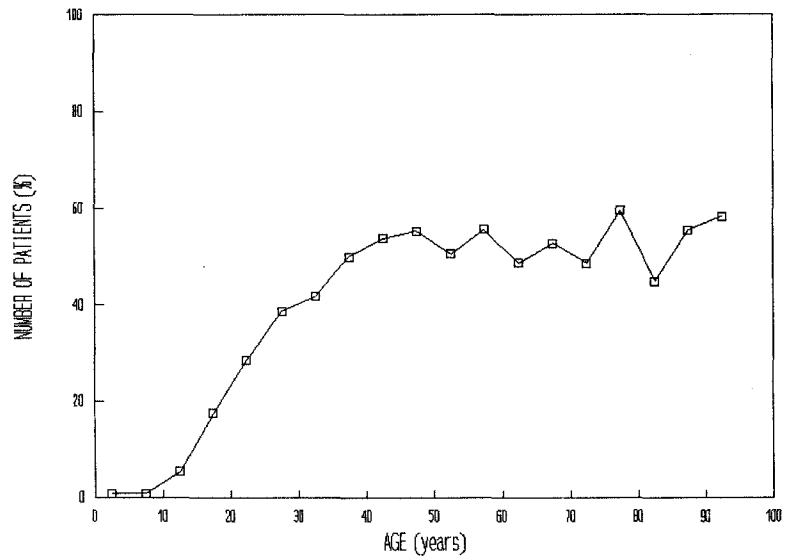
Table 2 *Influence of sex on prescription of benzodiazepines*

	Males (n=2,498; 43.1%)		Females (n=1,809; 56.9%)		P
Benzodiazepine users	1,067	(42.7%)*	841	(46.5%)*	<0.05
Number of beddays	22,272	(55.7%)†	17,713	(44.3%)†	
DDD per 100 beddays	51.2		52.8		
Hypnotic drug‡ users	692	(27.7%)*	602	(33.3%)*	<0.01

*Percentage within group.
†Percentage of total.
‡ATC codes N05CD, N05CF, N05CM.

▲ Figure 1
Proportion of patients with benzodiazepine prescription in relation to age

N05CF, N05CM), highly significant sex discrepancies were found: 27.74% for male and 33.28% for female users (p <0.01).

### Influence of age on benzodiazepine utilization and prescription

When looking at the prescriptions of oral benzodiazepines with respect to age, there was a progressive increase of the proportion of patients with benzodiazepines, from age 15 to 40, after which it remained fairly constant (Fig. 1). Benzodiazepine consumptions expressed in DDD per 100 beddays and related to patient age are shown in Figure 2. The overall benzodiazepine consumption was divided according to ATC code, in hypnotics (N05CD) and anxiolytics (N05BA). Because of similar therapeutic activities, classes N05CF (cyclopyrrolones) and N05CM were combined with hypnotics.

On the other hand, a proportion of 28.9 % of the patients were receiving a prescription for benzodiazepines only once, at night. This corresponded to a consumption of 23.45 DDD per 100 beddays. The data relating to this particular group of benzodiazepine users subdivided by age, are presented in Figure 3.

The median value of the age of benzodiazepine consumers was 59 years, higher than the median value of patients admitted.

Influence of the type of ward on benzodiazepine prescription and utilization

Table 1 shows that 44.3% of the patients were exposed to oral benzodiazepines during hospitalization. For both male and female patients, the type of ward had a marked influence on benzodiazepine utilization, the highest prescription rate being observed in surgical wards (58% of users), the lowest in mixed units (internal medicine/surgery) (17.5%). Benzodiazepine consumption on the different wards, expressed in number of DDD per 100 beddays, is presented in Table 3. The mean value was 59.08 DDD per 100 beddays with an SD of 47.52 DDD per 100 beddays. Large variations were observed between wards, from 0.23 DDD per 100 beddays in paediatry to 263.90 DDD per 100 beddays in the medical psychology unit.
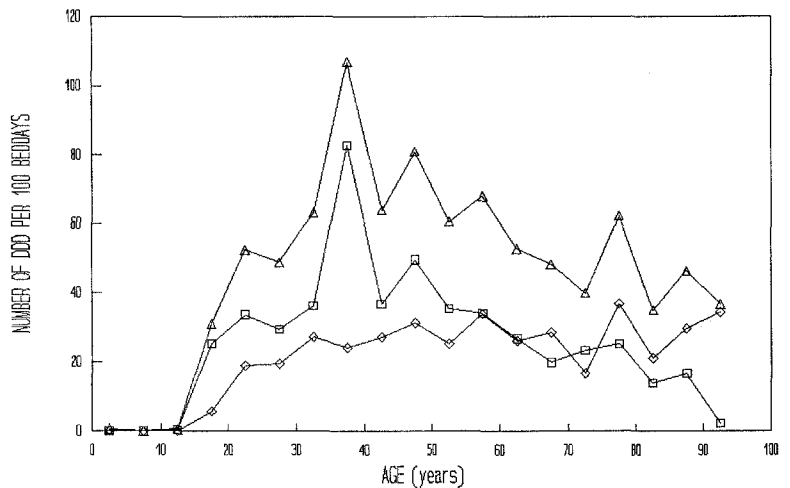
▲ Figure 2
Benzodiazepine utilization expressed in number of DDD (defined daily doses) per 100 beddays in relation to age. □: ATC class N05BA (anxiolytics); ◊: ATC classes N05CD, N05CF, N05CM (hypnotics); Δ: total

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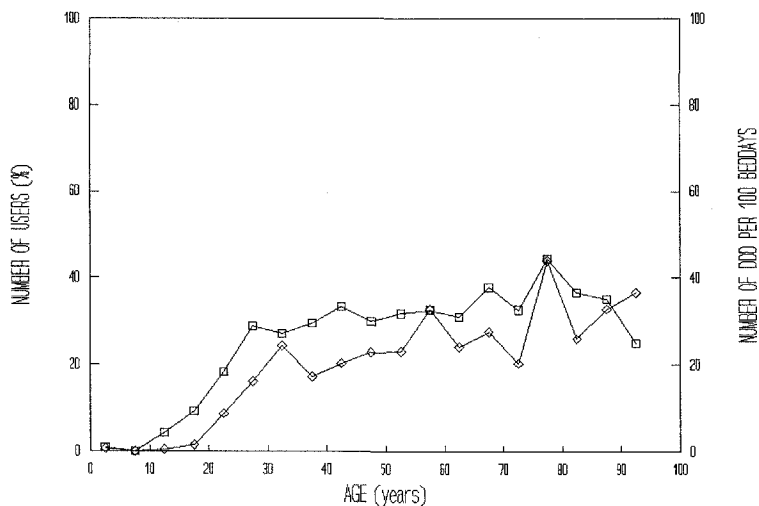
▲ Figure 3

Proportion of patients provided with one prescription of benzodiazepines at night only, in relation to age. □: proportion of users; ◊: DDD per 100 beddays

Table 3 Consumption of oral benzodiazepines expressed in DDD per 100 beddays in the different hospital units

Units	DDD per 100 beddays
Internal medicine	
• cardiology	50.44
• dermatology	50.77
• haematology	76.31
• nephrology	55.70
• neurology	65.11
• pneumology	38.08
• psychiatry	90.54
• medical psychology	263.90
• oncology/radiotherapy	36.36
• rheumatology	81.20
• metabolic disorders	35.23
Surgery	
• cardiac	33.10
• gastrointestinal	48.84
• general	52.10
• plastic	74.59
• orthopaedic	52.94
• neurosurgery	54.60
• urologic	23.47
Mixed	
• oral rehydration fluid	31.07
• ophthalmology	21.07
• paediatry	0.23
Intensive care	
• burns	79.44
• sterile	112.73
• cardiovascular surgery	31.74
• traumatic, neurosurgery	24.11
• internal medicine	39.47
• cardiology	94.80
Unknown	35.96
Median:	50.77
Range:	0.23-263.90

Important variations were also observed within the different groups of wards (medical, surgical, intensive care, etc.). However, by focusing the study only on oral benzodiazepine and neglecting parenteral administration, some bias will affect the consumption data. In addition to the present study, this bias was roughly estimated from another study performed in a 24-day period in 1993, including about 1,300 patient medication records (12,801 beddays), without distinctions for patient age and sex. During that period, the consumption of parenteral benzodiazepine (diazepam injection 10 mg, midazolam injections 5 and 15 mg) was measured and estimated at 7.23 DDD per 100 beddays on the wards.

Differences between the consumption of parenteral benzodiazepine in the various types of wards are shown in Table 4. As expected the highest consumption of parenteral benzodiazepine is observed in intensive care units where benzodiazepines are commonly used to obtain sedation and anxiolysis in a few patients.

During the same period, parenteral benzodiazepine consumption adds another 6.48 DDD per 100 beddays to the overall utilization, because of their use during technical interventions like surgery, endoscopy, coronary investigation and dilatation, etc. Although obtained in 1993 these results give valuable complementary information since the quantities of parenteral benzodiazepine supplied by the pharmacy in 1991 and in 1993 are almost equal (12.72 and 12.58 DDD per 100 beddays).

Comparative utilization of the various benzodiazepines

The total consumption of oral benzodiazepines in the hospital during the study periods was 53.95 DDD per 100 beddays, including 29.29 DDD per 100 beddays of anxiolytics (N05BA) and 24.66 DDD per 100 beddays of hypnotics (N05CD, N05CF, N05CM). Six products, lormetazepam (17.89 DDD per 100 beddays), flunitrazepam (3.20 DDD per

Table 4 *Mean consumption of parenteral benzodiazepines expressed in DDD per 100 beddays in the different types of service*

Type of service	Beddays	DDD per 100 beddays
Internal medicine	6,868	3.80
Surgery	4,526	5.65
Mixed	1,357	8.40
Intensive care	1,100	26.96

Table 5 *Comparative values of defined daily doses (DDD) and mean prescribed daily doses (PDD) during the study periods*

Benzodiazepine	ATC codes	DDD (mg)	PDD (mg)	PDD/DDD ratio
Diazepam	N05BA01	10.00	15.91	1.59
Oxazepam	N05BA04	50.00	23.00	0.46
Clorazepate	N05BA05	20.00	43.91	2.19
Lorazepam	N05BA06	2.50	2.46	0.98
Bromazepam	N05BA08	10.00	6.45	0.64
Prazepam	N05BA11	30.00	17.89	0.60
Alprazolam	N05BA12	1.00	1.15	1.15
Nitrazepam	N05CD02	5.00	4.70	0.94
Flunitrazepam	N05CD03	1.00	1.90	1.90
Triazolam	N05CD05	0.25	0.26	1.04
Lormetazepam	N05CD06	1.00	1.79	1.79
Loprazolam	N05CD11	1.00	1.40	1.40

100 beddays), both considered as hypnotics, alprazolam (8.92 DDD per 100 beddays), diazepam (7.61 DDD per 100 beddays), lorazepam (5.20 DDD per 100 beddays), and clorazepate (3.58 DDD per 100 beddays), classified as anxiolytics, represented 86% of the benzodiazepine consumption.

Comparison between DDDs and PDDs
Values of DDDs and PDDs of the various drugs are presented in Table 5. Differences were observed for 8 of the 12 used benzodiazepines. The DDD value underestimated the PDD in 4 of the 6 most used benzodiazepines. This finding reminds one that DDDs have to be considered as physical measure units of consumption and do not reflect the ratio of users when expressed in number of DDD per 100 beddays. The total number of DDD per 100 beddays was 54.05 whilst 43.3% of patients used benzodiazepine during the study periods.

Benzodiazepine utilization before admission
Considering the 50 randomly selected patients provided with a benzodiazepine prescription on the first day of hospitalization, the survey of the medical record confirmed that 62% of them were actually benzodiazepine users before admission. With respect to the study population, nearly 12.6% of the patients could be considered as benzodiazepine users before admission.

Benzodiazepine prescription at discharge
Of 50 randomly selected patients, non-users at admission but initiated to benzodiazepine usage during their hospital stay and benzodiazepine users up to discharge, 16 were actually discharged with a prescription of at least one benzodiazepine. Thus, with respect to our study population, it is expected that in about 6.8% of the patients discharged with a benzodiazepine prescription initiated in hospital, benzodiazepine consumption is induced by hospitalization.

Discussion
When looking at the overall prescription rate of benzodiazepine, the present study shows that the patient's sex has a significant influence on utilization but, in contrast to results published on consumption in general practice [1 2], differences are smaller. When focusing on hypnotic usage only, the study confirms a higher utilization amongst women (20% more than men). In any case, the differences were always smaller than those reported in the literature for the general population.

It is also interesting to analyse in detail the influence of the patient's age on benzodiazepine consumption or prescription. Depending on whether comparisons are made of the ratio of patients with and without prescription, or on the basis of true consumption (DDD per 100 beddays), results can lead to conflicting conclusions. The rate of prescription increases from the age of 15 and it is nearly stable beyond 35. However, when the utilization is expressed in DDD and weighted by the relative number of beddays, the overall consumption rises from the age of 15 up to 35-40, then progressively decreases for higher ages. By distinguishing between hypnotic and anxiolytic use according to the ATC codes, our results clearly show that the consumption of hypnotics, weighted by the number of beddays and, subsequently, by the number of users at different ages, remains fairly stable beyond the age of 35. Consequently, the observed peak of benzodiazepine consumption is mainly due to the high consumption of anxiolytic benzodiazepines by patients aged 35 to 50. This finding also emphasizes the poor indicative value of data when overall consumption of benzodiazepines in hospitals refers only to mean age and sex of patients. Moreover, results must be carefully interpreted when classifications of benzodiazepines in terms of hypnotics or anxiolytics are made. All benzodiazepines possess to some extent the two properties and, in practice, anxiolytic benzodiazepines are often used for their hypnotic effects. Never-

theless, our finding seems to be confirmed by consumption data observed with patients having received only a once a night prescription and by the parallelism between these data and those obtained according to hypnotic ATC codes.

It is obvious that the utilization of benzodiazepine is ward-dependent. Unfortunately, the design of the present study did not allow the assessment of rational or irrational prescription patterns. Comparison of benzodiazepine consumption per ward or type of ward, between hospitals, would be a valuable exercise to assess prescription patterns. On the other hand, large variations of consumption within and between wards, as shown in the present study, demonstrate that comparisons of benzodiazepine consumption between hospitals need to take into account the specific circumstances of each institution.

The method used to estimate the number of inpatients initiated in benzodiazepine usage after discharge is questionable because it is based on one user category (non-users at admission but users up to hospital discharge). It was found that roughly 6.8% of the admitted patients initiated a benzodiazepine usage during admission. This figure is high when compared to other results (1.6-2%) reported in the literature [7 8]. It reflects the high benzodiazepine consumption in Belgium. It also raises questions about benzodiazepine prescription habits in the hospital and their role in inducing medium- or long-term usage and subsequent dependence. Nevertheless, our findings are only indicative; they have to be viewed within the limits of a retrospective study conducted inside the hospital.

Regarding other aspects of the study, the ATC-DDD methodology was found to be appropriate and quite suitable despite existing differences between a few DDD's and PDD's. However, when utilization patterns are analysed, the combination of DDD data and prescription data is required to achieve a better understanding.

Conclusion

The main objectives of the present study were to establish a chart of benzodiazepine consumption and to determine the influence of patient-related and hospital-related parameters on their use. When considering the influence of patient sex, patient age and type of ward, the results showed that the utilization of benzodiazepines in the hospital was different from the use in general practice. This kind of drug utilization review is a potentially valuable tool for discussions with physicians and Pharmacy and Therapeutic Committees when trying to change prescription habits and to promote a more rational use of drugs in the hospital. In fact, more comparative studies with standardized methodologies are definitely needed to understand and assess the mechanisms of prescription patterns.

In a follow-up of the present study, action has been taken in the hospital to make physicians and nurses more perceptive to benzodiazepine prescription and to their possible role and capacity in inducing benzodiazepine consumption habits. Oral communications were presented and later an internal information bulletin was distributed to nursing and clinical staffs. No internal policies on benzodiazepine use have been established but simple guidelines were recommended.

- Whenever possible, look for alternative therapies with special regard to psychotherapy and information.
- In any case, individualize the benzodiazepine prescription and avoid ward prescription habits.
- Favour the "as needed" scheme to systematic repeated administrations.
- Inform the patient about benzodiazepine prescription and utilization.
- Assess regularly the need for benzodiazepine prescription.

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