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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

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The impact of hospitalisation on the initiation and long-term use of benzodiazepines

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Abstract *Background*: Inappropriate (long-term) use of benzodiazepines (BZDs) is a reason for concern. Several studies have suggested that hospitalisation may be a determinant for initiation of BZD use as well as for long-term use. However, the available evidence is conflicting.
Objective: To determine whether hospitalisation induces initiation of BZD use and subsequent long-term use.
Methods: A retrospective follow-up study was conducted. Randomly, 10,000 patients who had been hospitalised were selected (index date). Non-hospitalised patients, matched on age and gender, were sampled from the same living region and assigned the same index date as the corresponding hospitalised patient. Patients were included if adequate medication data were available from 18 months before to 18 months after the index date. Initiation of BZD use was defined as a prescription for a BZD or BZD-related hypnotic without a prescription for any of these drugs during the prior 6 months. Long-term use was defined as a period of consecutive use for at least 6 months following initiation.
Results: In this study, 8,681 hospitalised patients and an equal number of non-hospitalised patients were finally included. Overall, the relative risk for initiation of BZD use was almost twice as high [IDR 1.97 (95%CI 1.84–2.10)] among hospitalised patients as in non-hospitalised patients. This relative risk was most clearly elevated during the time window from 3 months before to 3 months after hospitalisation [IDR 4.81 (95%CI 4.08–5.67)]. The relative risk for long-term use during the entire 36-month observation period was not higher [IDR 1.04 (95%CI 0.95–1.13)] among hospitalised patients than among non-hospitalised patients. Within the time window of 3 months before and after hospitalisation, the relative risk for long-term use was significantly lower for the hospitalised group [RR 0.82 (CI 0.69–0.98)].
Conclusion: Our results confirm that hospitalisation is associated with an increased risk for initiation of BZD use; the risk is highest during the 3 months just before and after hospitalisation. However, hospitalisation appeared not to be a determinant for long-term use of BZDs.

Keywords Benzodiazepines · Hospitalisation · Prescription · Long-term use · Chronic disease score

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Introduction

Benzodiazepines are widely prescribed drugs for the treatment of several psychiatric disorders. Insomnia and anxiety are generally accepted indications for these agents. However, considerable controversy surrounds the use of benzodiazepines. These drugs are frequently used over longer periods of time, and this has been addressed in several studies [1, 2]. Long-term use has been associated with increased risk of dependence and withdrawal symptoms upon discontinuation [3, 4]. In the elderly, the use of benzodiazepines has been associated with an increased morbidity risk [5]. Short-term use is associated with an increased risk of injury-related mortality [6, 7]. It has been accepted that enduring benzodiazepine use is inappropriate for the treatment of anxiety states or insomnia [8].

Hospitalisation is often a major life-changing event that may provoke anxiety and insomnia; hospitalisation

itself can be a reason for initiation of benzodiazepine use. It has been suggested that benzodiazepine use started during hospital stay is an important factor for community use of these drugs. Howes et al. [9] found that of all hospital admissions of those not previously having taken benzodiazepines resulted in 23.6% receiving a prescription for a benzodiazepine for the first time in the hospital; and, in 5.3% of these patients, this resulted in a benzodiazepine prescription at discharge. First prescriptions do lead to more benzodiazepine prescriptions within a limited amount of time [10]. Although the impact of hospitalisation with regard to the initiation of benzodiazepine prescriptions has been well documented, data about the relationship between hospitalisation and benzodiazepine use remain conflicting and have not always addressed potential biases arising from possibly important confounders such as health status [11–15].

The objective of our study was to evaluate the possible association between hospitalisation and the initiation of benzodiazepine use in ambulatory care in the pre-hospitalisation and post-hospitalisation periods. Because hospitalisation may also lead to unnecessary long-term continuation of benzodiazepine use, we calculated the period of consecutive use of benzodiazepine use after the initial prescription and thereby also evaluated the possible association between hospitalisation and long-term use.

Methods

Setting

The setting of the study was the PHARMO record linkage system. PHARMO includes pharmacy-dispensing records from community pharmacies linked to hospital discharge diagnoses of all 950,000 community-dwelling residents of 25 population-defined areas in The Netherlands from 1985 onwards. This database has been described in full elsewhere [16]. In brief, the computerised drug dispensing histories contain information concerning the dispensed drug, dispensing date, the prescriber, amount dispensed, prescribed dosage regimen and the estimated duration of use. Drugs were coded according to the Anatomical Therapeutic Chemical (ATC) classification system for benzodiazepines (N05BA and N05CD) and benzodiazepine-related hypnotics and sedatives, i.e. zolpidem and zopiclone (N05CF). Patient information per prescribed medicine includes gender and date of birth. Each registered person is identified with an anonymous unique identification code that allows for the observation of patient medication use in time. The database does not provide information concerning the indication for use of the medicines nor the complete registration of non-prescription medicines as patients may also purchase these drugs from non-pharmacy outlets. The hospital discharge records are obtained from PRISMANT, previously known as the Dutch Centre for Healthcare Information (LMR Database), an institute that collates nationwide all hospital discharge records in The Netherlands since the 1960s into a standardised format. Relevant hospital data include the primary and secondary discharge diagnoses and data of hospital admission and discharge.

Study population

A retrospective follow-up study has been conducted. In this study, initially 10,000 patients who had been hospitalised (index date) between 1 July 1998 and 30 June 2000 were randomly selected from the PHARMO database. For each hospitalised patient, we sampled from the same living region a patient matched on age and gender, who had not been hospitalised during the same period. Patients were only included in this study if medication data for the time window of 18 months before and 18 months after the index date were available. Because of the lack of these medication data over the whole study period, some patients had to be excluded. The final study population consisted therefore of 8,681 patients and an equal number of matched non-hospitalised patients.

Outcome

Primary outcome was the initiation of benzodiazepine use which was determined within a time window of 18 months before and 18 months after the index date and was defined as a prescription for a benzodiazepine (ATC N05BA and N05CD) or benzodiazepine-related hypnotic or sedative (ATC N05CF) in this time window and not having had a prescription for any of these drugs in a time period of 6 months before that date. Secondary outcome was long-term use of benzodiazepines following the initial prescription. Long-term use was defined as a period of consecutive use of these drugs of more than 180 days as determined from the date of the initial prescription [17]. Patients were followed up until the estimated duration of use for the last benzodiazepine prescription for each individual patient with a maximum follow-up of 6 months.

Data analysis

The data were analysed in two ways; first incidence density rates and ratios of initiation of benzodiazepine use were calculated in the total study population as well as for the time window of 3 months before and after hospitalisation. We determined the number of first benzodiazepine prescriptions and calculated the incidence rate of first benzodiazepine prescriptions per 100 patient years. The incidence rate of the hospitalised group of patients was compared with the incidence rate of the non-hospitalised group. The relative risk was

expressed as the incidence density ratio (IDR), in which the non-hospitalised group was taken as a baseline risk. In order to assess the effects of other factors associated with patient and hospitalisation characteristics—namely age, gender, duration of hospitalisation, admission type, admission for surgery and differences in health status—we performed a stratified analysis in the time window of 6 months.

The health status was measured using the Chronic Disease Score (CDS). This is a measure of the chronic disease status among prescribed drug users and can be considered as an indicator of an individual's morbidity and overall health status. Valid measures of chronic disease status can be obtained from patients' medical records, but abstracting medical records is costly and difficult. The use of automated outpatient pharmacy databases appears to offer an increasingly available and low-cost approach to developing a measure of CDS. Exposure to various prescription drugs has shown to be a valid measure of certain chronic somatic diseases (e.g. insulin as a proxy for diabetes mellitus). The score ranges increase with the complexity of drug regimen as well as with the number and severity of 17 different chronic diseases [18–20]. Benzodiazepines and other psychotropic drugs are not included in the CDS.

Results

The study population consisted of 8681 hospitalised patients and an equal number of non-hospitalised patients. Table 1 provides the characteristics of the hospitalised patient group on the index date. Mean age was 52.6 years (SD 21.8) and 58.7% of the patients were female. The patients in the hospitalised group were using more medications than patients in the non-hospitalised group [CDS = 0 (42.2% versus 60.0%) and CDS ≥4 (30.7% versus 14.7%)].

During the entire study period, the incidence density (ID) of initial benzodiazepine prescription in the hospitalised group was 11.8 per 100 patient years (2436/20,613 patient years) and in the non-hospitalised group 6.0 per 100 patient years (1396/23,249 patient years). Initiation of benzodiazepine use was therefore twice [IDR 1.97 (95% CI 1.84–2.10)] as high in the hospitalised group as in the non-hospitalised group. In the hospitalised group, 16.8% of the total study group initially used anxiolytics and 11.2% hypnotics (Table 2); in the non-hospitalised group, these percentages were 10.7% and 5.4%, respectively. For both types of benzodiazepines, we therefore observed a similar increased risk of initiation of these drugs in the hospitalised group compared with the non-hospitalised group.

Figure 1 shows the monthly IDR for starting a benzodiazepine prescription during the study period of 36 months. The IDR was most clearly elevated during the time window of 3 months before and after hospitalisation [IDR 4.81 (95% CI 4.08–5.67)]. Table 3 presents in that time window of 6 months the association of hospitalisation and initiation of benzodiazepine use stratified by patient and hospitalisation characteristics. Incidence rates increased with age and duration of hospitalisation and were higher for men than for women. Patients with more medication (i.e. CDS ≥4) are more likely to receive a first benzodiazepine prescription.

The relative risk for long-term use (more than 180 days) during the entire 36-month period was slightly, non-significantly higher [RR 1.04 (95% CI 0.95–1.13)] among hospitalised patients than among non-hospitalised patients (58.5% of all initial benzodiazepine prescriptions in the hospitalised patient group were categorized as long-term medication versus 56.2% in the non-hospitalised group). Within the time window of 3 months before and after hospitalisation, the relative risk for long-term use was significantly lower for the hospitalised patient group [RR 0.82 (95% CI 0.69–0.98)].

Table 1 Characteristics of the hospitalised patient group (n = 8681) on the index date

Characteristic	n	%
Gender		
Male	3,588	41.3
Female	5,093	58.7
Age (years on index date)		
<65 years	5,557	64.0
≥65 years	3,124	36.0
Duration of hospitalisation		
1 day	417	4.8
2–5 days	4,374	50.4
>5 days	3,890	44.8
Admission type		
Emergency	3,966	45.7
Planned	4,715	54.3
Admission for surgery		
Yes	4,360	50.2
No	4,321	49.8

Discussion

In this study, we examined first benzodiazepine prescriptions not only after discharge from the hospital, but

Table 2 Benzodiazepines and benzodiazepine-related hypnotics as initial prescription

	Hospitalised (n = 8681)	Non-hospitalised (n = 8681)
Any	2,436 (28.1%)	1,396 (16.1%)
Anxiolytics (N05BA)		
Diazepam	579 (6.7%)	303 (3.5%)
Oxazepam	701 (8.1%)	519 (6.0%)
Other	181 (2.1%)	109 (1.3%)
Total	1,461 (16.8%)	931 (10.8%)
Hypnotics (N05CD and N05CF)		
Nitrazepam	71 (0.8%)	53 (0.6%)
Temazepam	684 (7.9%)	287 (3.3%)
Other	220 (2.5%)	125 (1.4%)
Total	975 (11.2%)	465 (5.3%)

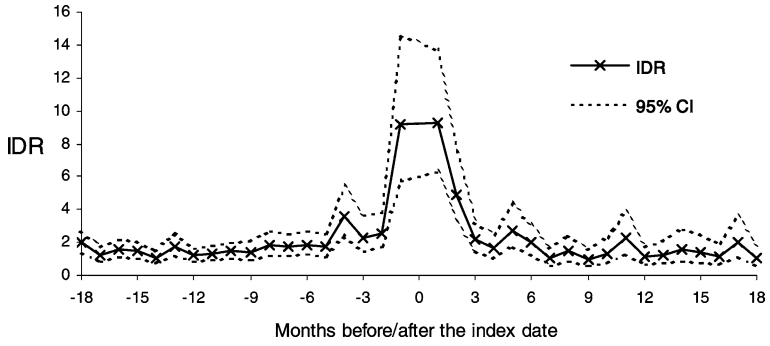

Fig. 1 Incidence density ratio (IDR) of initiation benzodiazepine use 18 months before and after hospitalisation compared with that in non-hospitalised patients

also during a pre-hospitalisation period. We calculated the monthly IDR for starting a benzodiazepine prescription over the whole study period of 36 months. One of the most interesting findings of this study is the strong association between hospitalisation and initial prescriptions of benzodiazepines in the time window of 3 months before and after admission with an IDR of 4.81. Our findings agree with several other studies, which have reported an association between hospitalisation and hospital-initiated and newly ambulatory prescribed benzodiazepines [9, 11–14]. In contrast to these studies, we were also able to assess the relationship between hospitalisation and newly prescribed benzodiazepines before hospitalisation. Problems with physical health can have an impact on mental health [21]. Accordingly, mental manifestations linked to an underlying physical disease may manifest first. Van Hulten et al. [21] found that benzodiazepines are a predictor for the onset of chronic disease. Probably deterioration of the health status, leading to later hospitalisation was the reason for starting benzodiazepines. We can therefore not conclude that hospitalisation causes (unnecessary) benzodiazepine initiation as has been suggested by others [14], but that the time period around a hospitalisation is associated with new benzodiazepine use. Further research is necessary to elucidate the underlying reasons for this fascinating pattern. Stratified analyses during the 3-month period before and after hospitalisation demonstrates that the risk of an initial benzodiazepine prescription was modified by patient and hospitalisation characteristics. Patients who use more medication (i.e. patients with a CDS ≥4) are more likely to receive a first benzodiazepine prescription. These findings agree with other studies, which have reported that benzodiazepine use is

Table 3 Results of starting benzodiazepine use during the time window 3 months before and after hospitalisation compared with those in non-hospitalised patients

	Hospitalised			Non-hospitalised			IDR (95% CI)
	No. of starts	Follow-up (patient years)	Incidence (per 100 patient years)	No. of starts	Follow-up (patient years)	Incidence (per 100 patient years)	
Overall	728	3,198	22.8	174	3,676	4.7	4.81 (4.08–5.67)
Gender							
Female	410	1,859	22.1	119	2,110	5.6	3.91 (3.19–4.80)
Male	318	1,340	23.7	55	1,566	3.5	6.76 (5.08–9.00)
Age							
<65	433	2,103	20.6	119	2,347	5.1	4.06 (3.32–4.97)
≥65	295	1,095	26.9	55	1,329	4.1	6.51 (4.88–8.68)
CDS							
0	257	1,447	17.8	89	2,257	3.9	4.50 (3.54–5.73)
1–3	227	851	26.7	62	896	6.9	3.86 (2.91–5.11)
≥4	244	900	27.1	23	524	4.4	6.18 (4.03–9.47)
Duration of hospitalisation							
				174	3,676	4.7	Reference
1 day	25	158	15.8				3.34 (2.20–5.08)
2–5 days	271	1,663	16.3				3.44 (2.85–4.16)
>5 days	432	1,377	31.4				6.63 (5.59–7.90)
Admission type							
				174	3,676	4.7	Reference
Emergency	357	1,453	24.6				5.19 (4.33–6.22)
Planned	371	1,745	21.3				4.49 (3.75–5.38)
Surgery							
				174	3,676	4.7	Reference
Yes	303	1,664	18.2				3.85 (3.19–4.64)
No	425	1,534	27.7				5.85 (4.91–6.98)

more common among subjects with poor health status [23]. Gender has been found to be a significant factor in predicting benzodiazepine use in many studies and is more prevalent among females [24, 25]. We observed the same pattern in the non-hospitalised group. However, we found in the period of 3 months before and after hospitalisation that the relative risk for benzodiazepine initiation was higher for men than for women.

We analysed the cumulative exposure months after the initial prescription. There was a significantly lower risk for long-term use of a benzodiazepine in the time window of 3 months before and after the hospitalisation date, compared with the whole study period. We could therefore not confirm findings of others that hospitalisation is also associated with (unnecessary) long-term use of benzodiazepines.

We need to consider the potential limitations of this study, when interpreting the present results. In this study, non-hospitalised patients were sampled from a group of subjects who were dispensed any drug during the study period. It is likely that this control group is in general less sick than the group of hospitalised patients, which could at least partly explain the increased use of benzodiazepines by this group. Therefore, we measured in both groups the chronic disease score and stratified on this (Table 3). This might, however, not have eliminated all differences in health status. Our definition of the initial prescription of a benzodiazepine (no prescription without a previous 6 months of use) might imply that several initial users could have been a previous user in prior months before our time window. That possibility might result in some misclassification and thereby a slight overestimation of our results. In conclusion, previous studies have raised much concern about hospitalisation-related initiation of benzodiazepine use and about long-term use of these drugs. The present study reveals that hospitalisation contributes to a clearly increased risk for initiation of benzodiazepine prescription. The risk is highest in the 3 months just before and after hospitalisation. Gender, age, chronic disease score and duration of hospitalisation are factors influencing the probability of starting with a benzodiazepine related to hospitalisation. We could not show an association between hospitalisation and the risk for long-term use.

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