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Original Article

DRUG UTILIZATION EVALUATION OF BENZODIAZEPINES IN A TERTIARY CARE HOSPITAL

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ABSTRACT

Objective: To assess the rationale use of benzodiazepines among various departments in a multi-speciality hospital.

Methods: A prospective study was conducted with a sample size of 200 for a period of six months. Data was collected from patients based on inclusion and exclusion criteria. Naranjo Adverse Drug Reaction Probability Scale and Drug Interaction Probability Scale (DIPS) were used as a study tool to measure the causality of adverse drug reactions and drug interactions. Based on the dosage of various benzodiazepines DDD was calculated and compared with WHO Anatomical Therapeutic Chemical (ATC) classification Defined Daily Dose (DDD).

Results: BZD's were mostly prescribed in males (74.5%) and married patients (86.5%) were more exposed to benzodiazepines compared to others. Lorazepam (70.1%) was found to be the most commonly used drug, mainly prescribed for sedation, followed by anxiety. DDD was calculated and majority of patients had DDD in accordance with WHO standard. Based on cost analysis, Clobazam was found to be the high cost and Lorazepam being the low-cost drug. The results of drug utilization evaluation of benzodiazepines study were compiled and reported to the respected department physician and their feedback was collected.

Conclusion: The study showed a rational utilization of benzodiazepines and the negative outcomes of BZDs can be reduced by providing drug-related information to the prescribers and consumers.

Keywords: Benzodiazepines, Drug utilization, Naranjo adverse drug reaction scale, DIPS, DDD

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INTRODUCTION

Drug utilization studies are used as a potential tool in the evaluation of health care system which has been conducted and major problems with respect to drug use patterns, prescribing behavior, gaps between guidelines were addressed. Benzodiazepines have long been used for conditions including various psychiatry disorders, insomnia, acute alcohol withdrawal and epilepsy [1]. Such studies help in optimizing the rational use of drugs in a clinical setting [2].

DUE implies the prescription of a well-documented drug in an optimal dose on the right indication, with correct information and at an affordable price. It also provides insight into the efficacy of drug use i.e. whether a certain drug therapy provides value for money.

Benzodiazepines (BZD) have become one of the most commonly prescribed classes of drugs due to their multiple therapeutic actions such as anxiolytics, sedatives, seizures, muscle relaxants and dependence syndrome [3].

Epidemiologic data from Europe, Canada, Japan and Australia indicate that rates of benzodiazepine use in the general population were found to be around 6%. It is reported that BZDs are often prescribed without any appropriate documentation for its use in the patients [3].

Off-label use is common in psychiatric patients where Clonazepam and lorazepam were reported to be the most frequently used drugs in an off-label manner [4].

One major explanation for the misuse of Benzodiazepines in the current scenario is lack of specific information regarding the adverse outcome of benzodiazepines and also about alternatives such as non-benzodiazepines sedatives [5]. BZDs are associated with various adverse effects either with long term or short term use and also the higher incidence of drug-drug interactions was reported among psychiatric patients [5, 6].

With limited duration and in lower doses, benzodiazepines usage was correlated with the improvement in the quality of life of the patients [7]. The present study aimed to assess the rationale of BZD usage by evaluating the prescription pattern and drug-related problems among various departments in a multi-speciality hospital.

MATERIALS AND METHODS

Study site

The study was conducted at PSG Hospitals, Peelamedu, Coimbatore.

Study approval

This study was approved by the Institution Human Ethics Committee (IHEC, PSG IMSR) of the hospital. The protocol was approved on 16/08/2018, Proposal number: 15/081. Patients or caretakers who were not willing to give informed consent were excluded from the study.

Study design

A prospective study of Drug Utilization Evaluation of Benzodiazepines was conducted to evaluate the prescription pattern, drug-related problems, indication, dose of the drugs and to assess the drug usage pattern using DDD.

Study period

The study was conducted for a period of 6 mo.

Study subjects

Various departments such a General Medicine, Cardiology, Gastroenterology, Psychiatry, Neurology, and Orthopedics were included in the study. Patients who were in the age group 20-80, prescribed with any formulation of benzodiazepines and were able to communicate were considered as an inclusion criteria, whereas pediatrics and outpatients were excluded from the study.

Data collection

Patients were approached in the respected departments based on the inclusion and exclusion criteria. After explaining about the study

in a regional language, consent form was collected from the patients prior to data collection. Data regarding the socio-demographic and clinical characteristics of the patients were obtained through interviews and past medical records.

From the drug chart review, current medications along with dosage, frequency, route of administration and duration of therapy have been recorded and assessed for drug interactions, adverse drug reactions, contraindications and also for the cost of the benzodiazepines therapy during the hospital stay. Follow up of patients will be continued till the patient is on BZD therapy during hospitalization or till discharge.

$$\text{DDD} = \frac{\text{Number of items issued} \times \text{Amount of drug per item (mg)}}{\text{WHO recommended DDD of drug}}$$

(Nachiya *et al.*, 2015) [8]

RESULTS

The study was conducted among 200 patients based on the inclusion and exclusion criteria.

Table 1 shows the baseline characteristics. The gender-wise distribution shows that out of 200 patients, 74.5% were male and 25.5% were female. Social habit depicts 25% were alcoholics, 7.5% were smokers, and 15.5% were both smoker and alcoholic. Married patients made up 86.5% of the total benzodiazepine prescribed population. Benzodiazepine prescription was more common among the employed patients which were 56.5% when compared to the unemployed.

Table 1: Baseline characteristics

Characteristics	No of patients (n)	Percentage (%)	P value
Gender			
Male	149	74.5	0.001
Female	51	25.5	
Social habits			
Smoker	15	7.5	0.03
Alcoholic	50	25	
Both	31	15.5	
None	104	52	
Marital status			
Single	25	12.5	0.796
Married	173	86.5	
Others	2	1	
Employment			
Employed	113	56.5	0.032
Unemployed	87	43.5	

In table 2 pattern of benzodiazepines usage is illustrated in which 70.1% were prescribed with lorazepam. Among six departments, cardiology department was found to have more benzodiazepine usage which was 44.5%. The most common clinical condition of patients treated with benzodiazepines was sedation, which was 40.3% followed by 36.3% of anxiety. 81.6% of patients did not develop any adverse drug reactions which were a high proportion while 18.4% developed ADRs. Drug interactions were not found in majority of the patients which showed 81.6%.

Table 2: Pattern of benzodiazepines usage

Characteristics	Lorazepam (n=141)	Chlordiazepoxide (n=12)	Clonazepam (n=25)	Alprazolam (n=12)	Diazepam (n=1)	Clobazam (n=10)	Total	P Value
Department, n (%)								
Cardio	87(43.2)	1(0.5)	0(0)	1(0.5)	0(0)	0(0)	89(44.5)	**0.000**
Ortho	0(0)	0(0)	0(0)	2(1)	0(0)	0(0)	2(1)	
Psych	31(15.3)	5(2.5)	17(8.5)	1(0.5)	1(0.5)	2(1)	57(28.5)	
Gen. Med	8(4)	3(1.5)	1(0.5)	0(0)	0(0)	0(0)	12(5.5)	
Neuro	6(3)	3(1.5)	3(1.5)	3(1.5)	0(0)	8(4)	23(11.5)	
Gastro	9(4.5)	0(0)	4(2)	5(2.5)	0(0)	0(0)	18(9)	
Clinical condition, n(%)								
Sedation	65(32.3)	2(1)	9(4.5)	3(1.5)	0(0)	2(1)	81(40.3)	**0.000**
Anxiety	44(21.9)	4(2)	11(5.5)	9(4.5)	1(0.5)	4(2)	73(36.3)	
Insomnia due to anxiety	22(10.9)	0(0)	1(0.5)	0(0)	0(0)	0(0)	23(11.4)	
Seizure	0(0)	0(0)	4(2)	0(0)	0(0)	4(2)	8(4)	
ADS	10(5)	6(3)	0(0)	0(0)	0(0)	0(0)	16(8)	
Drug related problems of BZDs: ADR, n(%)								
Definite	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	**0.000**
Probable	2(1)	1(0.5)	0(0)	0(0)	1(0.5)	2(1)	6(3)	
Possible	25(12.4)	1(0.5)	2(1)	1(0.5)	0(0)	1(0.5)	30(15)	
Doubtful	0(0)	0(0)	1(0.5)	0(0)	0(0)	0(0)	1(0.4)	
Nil	114(56.7)	10(5)	22(11)	11(5.4)	0(0)	7(3.5)	164(81.6)	
Drug Interactions, n(%)								
Highly probable	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	**0.001**
Probable	6 (3)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.5)	7 (3.5)	
Possible	13 (6.5)	1 (0.5)	6 (3)	5 (2.5)	0 (0)	4 (2)	29 (14.4)	
Doubtful	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.5)	1 (0.5)	
Nil	122 (60.7)	11 (5.5)	19 (9.5)	7 (3.5)	1 (0.5)	4 (2)	164(81.6)	

Table 3 shows the mean and median of benzodiazepines defined daily dose. In our study, the mean DDD of patients taking lorazepam 2 mg was found to be 2.6 which was exceeded when compared to the standard DDD which is 2.5. Similarly, the mean DDD of diazepam 10 mg was exceeded to 30 than the standard (10). 90 patients were prescribed with benzodiazepines in accordance with the WHO ATC standard.

Table 3: Mean and median of benzodiazepines defined daily dose

Drugs	Dose (mg)	n(%)	WHO ATC DDD (mg)	Mean DDD in mg(DDD)	Median DDD in mg(DDD)
Lorazepam	1	47(52.3)	2.5	1.4(0.57)	1(0.4)
	2	19(21.2)	2.5	2.6(1.045)	2(0.8)
Chlordiaze-poxide	10	2(2.2)	30	20(0.67)	20(0.67)
	20	2(2.2)	30	20(0.67)	20(0.67)
Clonazepam	0.5	5(5.5)	8	0.46(0.06)	0.48(0.06)
	1	1(1.1)	8	2(0.25)	2(0.25)
Alprazolam	0.25	2(2.2)	1	0.25(0.25)	0.25(0.25)
	0.5	7(7.8)	1	0.52(0.52)	0.5(0.5)
Diazepam	10	1(1.1)	10	30(3)	30(3)
Clobazam	5	1(1.1)	20	5(0.25)	5(0.25)
	10	3(3.3)	20	18.5(0.92)	18(0.89)

In table 4, Patients were divided into 2 groups, BZD prescription below 5 d and above 5 d. Under each group, mean dose of various generics of BZDs were calculated and compared between patients with ADR and without ADR in which positive correlation (p= 0.017) was observed with Lorazepam taking patients less than 5 d and negative correlation was observed in patients taking chlordiazepoxide and clobazam for more than 5 d and clonazepam less than 5 d.

Table 4: Comparison of ADRs based on mean dose of various generics of BZDs

Drug	5 D					Above 5 D				
	n (%)	ADR at dose (mg)	n (%)	No ADR at dose (mg)	p value	n (%)	ADR at dose (mg)	n (%)	No ADR at dose (mg)	p value
Lorazepam	19(9.5)	5.105	75(37.3)	4.973	0.017	8(4)	15.125	39(19.4)	11.897	0.130
Chlordiazepoxide	0(0)	0	7(3.4)	58.57	-	2(1)	60	3(1.5)	173.33	-0.688
Clonazepam	2(1)	1.5	16(8)	2.187	-0.266	1(0.5)	14	6(3)	4.42	0.946
Alprazolam	0(0)	0	6(3)	1.5	-	1(0.5)	5	5(2.4)	3.15	0.389
Clobazam	2(1)	40	3(1.5)	21.67	0.809	1(0.5)	80	4(2)	272.5	-0.570

Fig. 1 depicts the appropriateness of benzodiazepines based on defined daily dose were 55% had DDD more than the standard, 38.5% had DDD less than or equal to standard and DDD was not calculated for 6.5% patients.

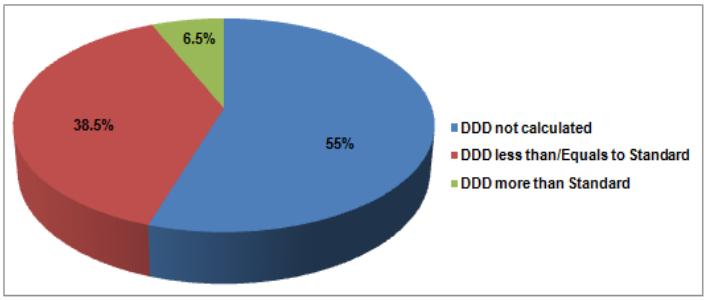

Fig. 1: Appropriateness of BZD's based on DDD

DISCUSSION

A study on drug utilization evaluation of benzodiazepines was conducted in a multi-speciality hospital to assess the rational use of benzodiazepines among 200 patients. In our study, benzodiazepines are prescribed more in males than in females, which is significant (p= 0.001) and the percentage of BZD was more in alcoholics [9]. These results were similar to the previous studies whereas a contrast to this was observed where the rate of benzodiazepine use was higher among women than men [15].

In our study BZDs were prescribed more in the married population as it is observed that married people undergoes more mental pressure than others [7]. The prescription of BZDs found to be higher in Cardio patients followed by psychiatry, as cardio patients are more likely to be anxious and restless about their condition illustrating the scientific rationale for BZD usage in people with heart disease. Lorazepam is the most commonly prescribed BZD in patients owing to its short-acting activity, which also improves both the emotional status and quality of life in patients.

The present study shows that BZD was mostly used for sedation followed by anxiety condition which is a contrast to the study conducted in 2016 in which BZDs were mainly used for anxiety (44.4%)[10,16]. As majority of patients in the present study were from cardiology department, insomnia may contribute as a risk factor for developing high blood pressure, CHD and heart failure [11]. Overall, 64.1% patients were prescribed with 4 to 6 d of BZDs and the BZD prescription increases with the lengthening of hospital stay.

Table 2 shows that 18.4% of patients have developed ADR such as drowsiness and dizziness. ADRs were frequently found in patients taking Lorazepam which was similar to the previous study as it results in the direct extension of CNS depressant properties [12, 13]. Interventions were made through clinical pharmacists in 11% of patients by stopping the drug in 8% and by dose reduction in 3%.

On assessing the Drug-interaction, it depicts that interactions were identified in 18.5% patients where Lorazepam showed a higher rate of drug interactions which was identical to the previous study [14]. Out of 200 patients, only one patient was admitted with BZD dependence syndrome and was treated with long acting BZD (Diazepam) during our study period.

DDD per patient is calculated in patients prescribed with BZDs for its main indication as anxiolytics and anti-epileptics. Considering WHO ATC DDD as a standard reference, it showed 38.5% of patients were prescribed in accordance with that and 6.5% of patients showed inappropriate use (exceeded the standard DDD), fig. 1.

From table 3, it is found that DDD of patients who were taking Lorazepam 2 mg (2.6 mg) exceeded the standard DDD (2.5 mg) which can be avoided by dose reduction. The mean and median of DDD/patient was found to be 5.64 and 2. In an average hospital stay of 6 d a patient was exposed to 5.64 DDD's which is found to be rational.

The study shows that benzodiazepines were continued after discharge in 31.3%. Drug related problems during discharge were analyzed in which 5.47% had developed ADR and 6% had drug-drug interactions during their hospital stay.

Table 4 shows that patients who are taking lorazepam less than 5 d found to be significant(p= 0.017) on positive correlation whereas insignificant result was seen in more than 5 d of Clonazepam, Alprazolam and lorazepam prescription. This depicts that ADRs are dose dependent in patients taking Lorazepam independent of the duration of BZD prescription.

From our study, Clobazam was founds to be the high cost BZD compared to others. But while considering the duration of therapy, it showed that Chlordiazepoxide contributed 45% and Lorazepam being the low cost drug contributed 70.1% to the overall BZD prescription indicating a rational utilization of drugs.

Through Feedbacks obtained from the physicians, it is identified that Lorazepam was the drug of choice followed by Alprazolam and Clonazepam. Benzodiazepines were prescribed as short term for insomnia and anxiety and as long term for alcohol withdrawal and seizure. 5 out of 6 physicians suggested mental status examination in patients before prescribing BZDs except in cardiology where 61.7% of BZDs were prescribed, which can be considered to avoid over usage. The limitation of the study was Defined Daily Dose was not available for all the benzodiazepines.

CONCLUSION

Lorazepam was founds to be the commonly prescribed drug due to its beneficial action compared to other benzodiazepines and its usage was found to be more among cardio patients for short term. Dose dependent ADR was significantly identified in patients taking Lorazepam. More studies are required to validate this causation of dose dependent ADR in other BZDs. Drug related problems can be reduced with the more appropriate dose and by switching to non-BZDs sedatives at the time of discharge. Since WHO ATC/DDD values are based on international data it is confined with certain limitations for considering it as a reference value. A safe, effective and optimum therapy can be provided to the patient by minimizing the negative outcomes and thereby ensuring the rationale in its use.

AUTHORS CONTRIBUTIONS

Conceived and designed the study: P. Rama, P. Janani, R. Monisha, Susan Varghese Paul and Varsha Elsa Scaria. Performed the study: P. Janani, R. Monisha, Susan Varghese Paul and Varsha Elsa Scaria. Contributed materials/analysis tools: P. Rama, P. Janani, R. Monisha, Susan Varghese Paul and Varsha Elsa Scaria. Manuscript preparation and correction and Correspondence: R. Monisha, Susan Varghese Paul and Varsha Elsa Scaria. Peer support: Saloni Krishna

CONFLICT OF INTERESTS

Declared none

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