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## **Prescription Pattern of Benzodiazepines for Inpatients at a Tertiary Care University Hospital in Pakistan**

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### **Abstract**

**Objective:** To determine the point prevalence of benzodiazepine prescriptions for inpatients at a tertiary care university hospital in Pakistan and to correlate it with prescription patterns of various specialties, indications and demographic variables of the patients.

**Methods:** This 24-hours point prevalence study was done at The Aga Khan University Hospital, Karachi. By convenient random sampling, 208 inpatients were interviewed. Patients' files were also studied to record the drugs administered. Data was entered into questionnaires and analyzed by SPSS 10.0.

**Results:** The point prevalence of the benzodiazepines was 21.2%. It was higher among males than females and among surgical than non-surgical patients. Midazolam was the most commonly used benzodiazepine, followed by Alprazolam and Lorazepam. Pre-anesthesia and psychiatric symptoms were the two most common indications. Oral route was used in 84% patients for drug administration and mean Valium equivalent dosage was 4.86mg/day. Mean length of prescription was 3 days. Longer duration of hospitalization was a significant predictor of the requirement of benzodiazepine prescription (p-value=0.020).

**Conclusion:** Prescription pattern of benzodiazepines at a tertiary care university hospital is similar to that reported in the developed countries through monitoring at various levels by physicians, clinical pharmacist and nursing staff. Data regarding the prescription pattern of benzodiazepines is scarce, and it needs to be expanded to formulate clear guidelines regarding their prescription (JPMA 55:259;2005).

### **Introduction**

After discovery of first Benzodiazepine, Chlordiazepoxide, in 1957, a large number of similar compounds were quickly introduced in clinical practice, being the most successful drugs ever used.<sup>1</sup> The most important differences among the variety of benzodiazepines are pharmacokinetic ones. Established indications are anxiety and sleep disorders, seizures, epilepsy, muscle-relaxation, induction of amnesia, pre-medication and sedation in emergency medicine. In recent years it has

also been proven to be effective in the treatment of panic disorder and catatonia.<sup>2</sup>

Benzodiazepine compounds have become an accepted component in the lives of a large segment of our population.<sup>1</sup> They are among the most prescribed and consumed medication groups in the world<sup>3</sup> having a multifactorial action with social and psychological roots<sup>4</sup> and often not fully supported by present state of scientific knowledge.<sup>1</sup> Benzodiazepines are widely prescribed in the

hospital setting in the absence of appropriate documentation.<sup>4</sup>

The long-time benzodiazepine use by a considerable part of the population and its adverse consequences such as somatic and cognitive side effects, interactions with other drugs and alcohol and its possible impairment of quality of life has provoked a critical discussion about the practice of prescribing benzodiazepine and the information provided by physicians.<sup>5</sup> The existence of Benzodiazepine dependence was described in the early sixties with very high dose of chlordiazepoxide but it has become a real concern for the medical community since the late seventies with increasing number of reports of withdrawal symptoms.<sup>6</sup> Patients taking these drugs for four months or more may develop symptoms of withdrawal, characterized by anxiety, dysphoria, malaise, depersonalization, and by perceptual changes such as hyperacusis and unsteadiness.<sup>7</sup> According to several studies, Benzodiazepine overdose is the most common way of self-poisoning among the substance induced suicidal attempts accounting for 30%-40% in western literature<sup>8,9</sup>, but 80% in Pakistan due to availability of the drugs over the counter, a fact which can be generalized to most developing nations.<sup>10</sup>

According to a study by Gutierrez et al<sup>5</sup>, in-patients on benzodiazepines in department of internal medicine of a hospital were followed for one year. Fifty percent of the patients prescribed Benzodiazepine for the first time were taking the drug even after one year. Moreover, a local study done on in- and out-patients revealed that in 73.4% drug prescriptions, duration of treatment was not specified.<sup>11</sup> Thus iatrogenic induction of benzodiazepine dependence is an issue, which needs immediate attention and intervention.<sup>12,13</sup>

A study was conducted at The Aga Khan University Hospital to establish the prescription pattern of Benzodiazepines among in-patients, to determine the common types used, most common indications and any possible associations of usage with the patient's demographic data and hospital settings.

## Methods

This was a 24 hours cross-sectional study conducted at The Aga Khan University Hospital, Karachi. The data was collected from in-patients of Surgery, Medicine, Obstetrics & Gynecology, Paediatrics, Psychiatry, Day-Care and Private wards on principle of convenient random sampling. Seven fourth year medical students of The Aga Khan University collected the data on a single working day. The information was entered on a questionnaire specifically designed for the study. Three types of questions were asked in the questionnaire, patient socio-demographic data, hospital-settings and prescription of benzodiazepines during the stay in hospital. Socio-demographic data included patient's

hospital record number, gender, age, marital status, profession, education, place of residence and monthly household income. Hospital setting information consisted of ward, physician in charge, admitting service, primary diagnosis and length of stay. Benzodiazepine prescription information included questions about the indication, type, dosage, frequency and route of administration and length of benzodiazepine administration in days including the day of data collection. The questions were answered by the patient themselves or their attendants. The information about the prescriptions was confirmed from the medical records and online pharmacy system to minimize the recall bias regarding the prescription of the drug. All members of the survey team sought informed consent from the patients or their attendants according to an approved protocol.

Data was entered in SPSS 10.0 (Statistical Package for Social Sciences 10.0) and same software was used for statistical analysis of the data to establish the prescription pattern of Benzodiazepines. Student's t-test and chi-square test were used to determine any association between the patient's data and need for the benzodiazepine prescription. A p-value of <0.05 was considered as the criteria of statistically significant association in all the cases.

## Results

Of the 375 patients admitted on the study day, 208 were included. There were 53.70% females and the mean age of the participants was 39.53 years. Of the total subjects, 64% were married, 27.1% single, 7.9% widowed and 1.0% divorced. There were 28.9% participants without any formal education. The mean and median monthly household income was Rs.26,200 (US\$ 450) and Rs. 10,000 (US\$ 175) respectively. Professionals and labourers were 10.8% each, businessmen and students were 8.7% each, 6.7% were retired and 12.3% could not be put in any category, with the reason being that the patient was too young to have a profession or be a student. Non-residents of Karachi comprised 19.5%. Mean length of admission at the hospital of the overall population was 6 days. These socio-demographic characters of the population are described in the first column of Table 1.

Out of 208 patients enrolled in the study, 44 (26 males, 18 females) were prescribed benzodiazepines on the study day. Thus the point prevalence of the benzodiazepine prescription at AKUH was 21.2%. The prevalence of benzodiazepine prescription among males and females was 27.37% and 16.36% respectively and that among surgical and non-surgical patients was 25.58% and 18.03%, respectively. Mean age of the patients prescribed benzodiazepines was 40.3 years. The mean length of hospitalization among them was 9 days. The characteristics

**Table 1. Description and comparison of in-patients' characteristics who were prescribed Benzodiazepines and those who were not prescribed Benzodiazepines.**

	Total (n=208)	Prescribed (n=44)	Not Prescribed (n=164)	p-value
<b>Gender %</b>				
Male/Female	46.3/53.7	59.1/40.9	42.9/57.1	0.056
<b>Age (years)</b>				
Mean	39.5	40.3	39.3	0.799
<b>Marital status %</b>				
Married	64.0	57.1	65.8	0.296
Un-married	36.0	42.9	34.2	
<b>Income %</b>				
<Rs.10,000	53.8	66.7	51.0	0.424
Rs.10,001-50,000	34.2	23.8	36.5	
>Rs.50,000	12.0	9.5	12.5	
<b>Education %</b>				
Nil	28.9	25.0	29.9	0.953
Primary	21.1	22.5	20.8	
Secondary	13.4	12.5	13.6	
Intermediate	10.8	10.0	11.0	
Graduates	17.5	22.5	16.2	
Postgraduates	8.2	7.5	8.4	
<b>Profession %</b>				
Housewives	37.4	25.0	40.7	0.293
Laborers	10.8	15.0	9.7	
Professionals	10.8	7.5	11.6	
Businessmen	8.7	10.0	8.4	
Students	8.7	17.5	6.5	
Retired	6.7	10.0	5.8	
Unemployed	3.1	5.0	2.5	
Landlords	1.5	2.5	1.3	
Others	12.3	7.5	13.5	
<b>Residence %</b>				
Karachi	80.5	75.0	81.9	0.323
Outside Karachi	19.5	25.0	18.1	
<b>LoA* (Days)</b>				
Mean	6	9	5	0.020
<b>Service %</b>				
Surgical	41.3	50.0	39.0	0.189
Non-surgical	58.7	50.0	61.0	

\*LoA: Length of admission

of the patients prescribed benzodiazepines are also described in the second column of Table 1.

The most commonly prescribed benzodiazepine was Midazolam in 65.9% cases, followed by Alprazolam and Lorazepam in 11.4% each. Other benzodiazepine generics prescribed and proportion of different Benzodiazepines in

terms of their pharmacokinetics are shown in Table 2. Mean Valium equivalent daily dosage of the drug among patients was 4.86mg/day. Mean length of benzodiazepine administration was about 3 days. In 84.1% cases the drug was administered orally while in the remaining 15.9% cases it was administered intravenously.

**Table 2. Prescription pattern of benzodiazepines.**

<b>Type [%]</b>	
Midazolam	65.9
Alprazolam	11.4
Lorazepam	11.4
Temazepam	4.5
Bromazepam	2.3
Clonazepam	2.3
Lormetazepam	2.3
<b>Duration of Action [%]</b>	
Short Acting	63.6
Intermediate Acting	31.8
Long Acting	4.6
<b>Valium equivalent daily dosage [mg]</b>	
Mean	4.86
Median	3.35
<b>Route of Administration [%]</b>	
Oral	84.1
Intravenous	15.9
<b>Length of prescription [days]</b>	
Mean [Range]	3 [1-10]
Median	1
Mode	1

Major indications for benzodiazepine prescription were pre-operative sedation and amnesia (40.9%) and in 9.1% of the cases the reason could not be established. These indications are described in Table 3.

Socio-demographic and hospital data was correlated with the need for prescription of benzodiazepine drugs. Association was sought between Age, Gender, Marital status, Profession, Monthly Household Income, Education, Residence, Surgical or non-surgical services and Length of admission at the hospital with Benzodiazepine prescription. Among these, length of admission at the hospital proved to be a significant predictor for benzodiazepine prescription (p-value 0.02). The summary of these findings is summarized briefly in last column of Table 1.

## Discussion

The point-prevalence of Benzodiazepine prescription among inpatients was 21.2%. The prevalence among males in our study was higher than in females, which is contradictory to most studies carried out in community.<sup>12</sup> However our result was in harmony with studies done among inpatients.<sup>13</sup> The review of literature<sup>4,14,15</sup> confirms that the prevalence of benzodiazepine prescription at AKUH is comparable to that anywhere in the world, in fact being lower than most of the reported prevalence. However, very little

**Table 3. Means of benzodiazepine prescription.**

<b>Indications for Prescribing Benzodiazepines (n=44)</b>	
Pre-operative sedation	40.9%
Psychiatric Symptoms	20.5%
Neurological diseases	9.1%
Malignancy	6.8%
Minor invasive procedures	6.8%
Other medical conditions	6.8%
Indications not established	9.1%
<b>Admitting Services of Patients</b>	
<b>Prescribed Benzodiazepines (n=44)</b>	
Internal medicine	22.7%
Orthopedic Surgery	18.2%
General Surgery	9.1%
Urology	6.8%
Other surgeries	9.1%
Oncology	6.8%
Pediatrics	11.4%
Psychiatry	11.4%
Obstetrics and gynecology	4.5%
<b>Percentage of Patients Prescribed Benzodiazepines in a ward (n=208)</b>	
C0 - Psychiatry ward	62.5%
D0 - Pediatrics ward	16.7%
B1 - Surgery ward	6.5%
C1 - General Medicine ward	40.0%
D1 - Day Care Surgery ward	80.0%
A2 and B2 - Obstetrics & Gynecology ward	Nil
C2 - Medicine ward	10.0%
ICU - Intensive care unit	40.0%
P1, P2 and P3 - Private ward	21.4%

comparable data could be found from the local literature. It is noteworthy that most of the studies considered here are reporting the prevalence in developed countries, where the prescription of benzodiazepines is considered well regulated. Little data is available regarding developing countries.

In our study, Midazolam, a short acting benzodiazepine was most commonly prescribed, the indications being preoperative sedation and anterograde amnesia. Alprazolam and Lorazepam, both intermediate acting, followed Midazolam and most frequent indication for these two were psychiatric symptoms like anxiety, insomnia, agitation and depression. There is remarkable discrepancy between the proportions of various types of benzodiazepines prescribed and their duration of action in different studies.<sup>4,16</sup> Summers et al report majority of the benzodiazepines prescribed were long acting (55%) and

intermediate-acting (20.7%), despite the fact that most indications (pre-anaesthetic and night-time sedation; total 71.6%) called for the shorter-acting drugs. This inconsistency seems to shadow the indications of individual benzodiazepines. Moreover, in our study as well as others<sup>4</sup>, indication for benzodiazepine usage could not be established in many cases. This clearly suggests that at most places regulation of benzodiazepine prescription is either non-existent or not implemented in its true spirit.

In our study, benzodiazepines were prescribed more frequently by the surgeons than the physicians, psychiatrists or oncologists. However, this difference was not statistically significant. Zisselman et al also obtained similar results.<sup>4</sup> The oncologists require palliative treatment so . Surendrakumar et al showed same proportion of benzodiazepine prescriptions from oncologists as in our study.<sup>17</sup>

No significant association has been documented between age, gender, marital status, economic conditions and the requirement for benzodiazepines.<sup>20,21</sup> Neuropsychiatric disorders, ethnicity and length of hospitalization play an important role.<sup>4,16</sup>

In our study, only the length of admission to the hospital was a statistically significant predictor for benzodiazepine prescriptions. This can be attributed to the physical, emotional and financial constraints, during prolonged hospitalizations, causing anxiety.

There is a dire need to analyzed the prescription pattern of benzodiazepines to regulate their usage, more so in third world countries, where these drugs are available over the counter. More studies correlated with the indications of the individual types of benzodiazepines, would help to formulate guidelines for prescribing this group of drugs for various indications. Many studies have successfully reported the decrease in the benzodiazepine prescription by effective strategies<sup>18-22</sup>, which can be duplicated in most settings. Another concern is the dependence potential of the benzodiazepines, prescribed for the first time in hospital and continuing the prescription at discharge indefinitely, which has been confirmed in various studies.<sup>15-23</sup> All these matters can only be solved in the presence of substantial and convincing data, which can steer the policies to regulate the prescription of benzodiazepines at all levels and their effective implementation.

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