

DRUG UTILIZATION STUDY OF BENZODIAZEPINES BASED ON WHO CORE DRUG USE INDICATORS IN AN OUTPATIENT DEPARTMENT OF A TERTIARY CARE HOSPITAL IN EASTERN UTTAR PRADESH, INDIA

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Received: 10 March 2025, Revised and Accepted: 22 April 2025

ABSTRACT

Objective: To analyze the drug utilization pattern of the benzodiazepines being prescribed at our hospital by calculating various parameters defined by the World Health Organization as core drug use indicators.

Methods: This cross-sectional study has enrolled 388 patients receiving one drug from the benzodiazepine group coming to the Psychiatry Outpatient Department in a tertiary care hospital in Eastern Uttar Pradesh. The drug consumption pattern of benzodiazepines was analyzed by calculating the defined daily dose (DDD) per 1,000 inhabitants per day, the prescribed daily dose (PDD), and the PDD to DDD ratio.

Results: Out of 388 patients enrolled in the study, most subjects were females. Regarding age group, most of the study participants belong to the 30–40 years age group, followed by 18–30 years. Most of the participants were suffering from depression with anxiety, followed by anxiety alone. The most commonly prescribed medicine in this study was clonazepam, followed by lorazepam. Alprazolam (anatomical therapeutic chemical code N05BA12) had a PDD/DDD ratio of 0.425. Chlordiazepoxide (N05BA02) had a PDD/DDD ratio of 0.425. Clobazam (N05BA09) showed a relatively higher PDD/DDD ratio of 0.792. Clonazepam (N03AE01) exhibited a notably low PDD/DDD ratio of 0.059. Lorazepam (N05BA06) had a PDD/DDD ratio of 0.713. The PDD/DDD ratio of all the prescribed benzodiazepines in this study was <1.

Conclusion: This study concludes that the prescribed benzodiazepines were appropriate for their indications, and the PDD and its ratio with DDD reflect the appropriate utilization of benzodiazepines for its indication.

Keywords: Anatomical therapeutic chemical classification code, Defined daily dose, Prescribed daily dose, Drug utilization pattern, Benzodiazepines.

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INTRODUCTION

The concern and challenges for mental health illness are sloping upward in almost all parts of the world as it affects not only the individual but also has social and economic considerations, so the health-care community, as well as various governments and non-government agencies, are giving high priority to mental health illness [1,2]. For the treatment of mental health illness, antidepressants, atypical antipsychotics, and benzodiazepines are used mostly [2].

Since its introduction in the early 1960s, benzodiazepine has diversified therapeutic indications. They are most commonly prescribed psychoactive medications across the globe in different age groups of patients suffering from various mental disorders, especially in the management of anxiety and insomnia as anxiolytics along with this they are also indicated for the treatment of panic attacks, phobias, obsessive-compulsive disorders and seizures [3].

Benzodiazepines are comparatively safe, efficient, fast-acting medications that produce and maintain sleep by having a calming effect on the patient with minimum side effects on short-term usage [4]. However, long-term administration of benzodiazepines can have various adverse effects, such as dementia, excessive sedation, a decline in cognitive functions, tolerance, and dependence [5]. Due to the adverse effects associated with long-term usage of benzodiazepine, an efficient drug utilization study can help to understand the pattern of its usage among the population being treated for mental health illness [6].

As per the World Health Organization's 1997 definition, drug utilization research refers to the study of marketing, distribution, prescription,

and use of medicines in a society with special emphasis on the resulting medical, social, and economic consequences. Drug utilization research plays an important role in policy formulation at local and national levels by providing feedback regarding the usage pattern of drugs in clinical practice [7]. Depending upon the patient characteristics, the prevalence of the disease in the region, existing sociodemographic patterns, medicine availability, and clinician's choices among the various available medicines in the population subset they are catering to modifies the drug utilization practices [6]. The ultimate objective of drug utilization research is resource optimization based on their availability at the local and national levels and promoting the rationale use of medicines [7].

The reference standard for drug utilization research is the World Health Organization anatomical therapeutic chemical/defined daily dose (ATC/DDD) methodology. Various studies have been done regarding drug utilization patterns in different health-care specialties in India. This study was done to analyze the consumption pattern of benzodiazepines based on WHO core drug use indicators.

METHODS

This cross-sectional study was carried out in the psychiatry outpatient department (OPD) of a tertiary care hospital in eastern Uttar Pradesh for a period of 6 months. The study was commenced after getting approval as per the letter no IEC/2024/22 from the Institutional Ethics Committee of Maharshi Devraha Baba Autonomous State Medical College, Deoria. Informed consent was taken from the enrolled patients to ensure the informed participation of the patients. In this study, patients' demographic details and the relevant data were collected in a pre-designed, pre-approved case record form for evaluation.

Inclusion criteria

1. Patients receiving at least one drug of the benzodiazepine group
2. Patients are willing to participate in this study and have given their consent.

Exclusion criteria

1. Patients aged <18 years or more than 60 years of age
2. Patients receiving more than one benzodiazepine
3. Patients receiving any other drug which has a synergistic effect when given with benzodiazepine.

Statistical analysis

Microsoft Office Excel 2010 was used for the evaluation of data. Representation of results was done using descriptive statistics (percentage, mean \pm standard deviation, tables, and graphs).

RESULTS

A total of 388 prescriptions from patients with a diagnosis of psychiatric disorder and receiving at least one benzodiazepine drug prescribed from the psychiatry OPD were enrolled, and data collected from them was analyzed. As per the ATC Classification code of the benzodiazepines prescribed in this study, DDD was taken into account for the calculation of the prescribed daily dose (PDD)/DDD. For the calculation of DDD per 1,000 inhabitants per day (DID), the population of the Deoria district was taken into consideration as per 2011 census data as almost all the patients treated belong to the Deoria district.

The distribution of cases according to age among the 388 study participants showed that the majority belonged to the 30–40 years age group, accounting for 32.5% (n=126) of the total cases. This was followed by the 18–30 years age group, which comprised 29.6% (n=115) of the cases. The 40–50 years age group represented 19.8% (n=77) of the cases, whereas the 50–60 years age group accounted for 18.0% (n=70), as reflected in Fig. 1. This distribution indicates that the majority of the cases were in the younger and middle-aged population, with a decline in case numbers in the older age groups.

Among the 388 study participants, the majority were female, accounting for 67.3% (n=261) of the cases, whereas males comprised 32.7% (n=127) as per Fig. 2. This indicates a higher prevalence of cases among females compared to males.

The majority of the participants, 97.4% (n=378), had no significant past medical history or ongoing medication use. However, 1.5% (n=6) reported a history of hypertension, whereas 0.5% (n=2) had hypothyroidism. In addition, a small proportion of participants had undergone cholecystectomy (0.3%, n=1) or had a history of seizure disorder (0.3%, n=1), as reflected in Table 1 and Fig. 3.

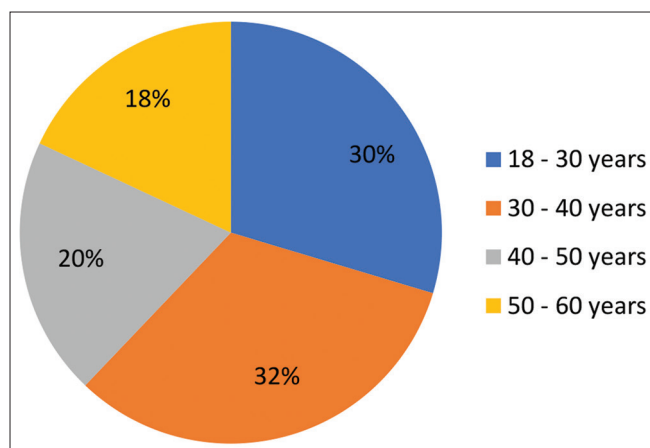


Fig. 1: Pie chart reflects the distribution of patients (n=388) as per the age groups

The most common primary complaint or diagnosis among participants was depression with anxiety (67%, n=261). Anxiety was reported in 19% (n=72) of cases, whereas anxiety and migraine accounted for 5.9% (n=23). A smaller proportion of participants had seizure disorder (1.3%, n=5) and alcohol withdrawal syndrome (2.1%, n=8). In addition, depression with insomnia (1.0%, n=4), bipolar disorder with anxiety (0.8%, n=3), schizophrenia with insomnia (0.8%, n=3), and insomnia (1.3%, n=5) were reported. Other conditions were noted in 1.0% (n=4) of cases, as mentioned in Table 2 and Figs. 4 and 5.

As reflected in Table 3, the number of drugs prescribed varied among participants, with the majority (39.2%, n=152) receiving more than five medications. Three drugs were prescribed in 27.1% (n=105) of cases, followed by four drugs (13.7%, n=53) and two drugs (12.1%, n=47). A smaller proportion received five drugs (7.2%, n=28), whereas only 0.8% (n=3) of participants were prescribed a single medication.

Among the benzodiazepines prescribed, clonazepam was the most frequently used, accounting for 82.7% (n=321) of cases. This was

Table 1: Distribution of cases (n=388) according to past history of illness and medications

Past history of illness and medications	No.	Percentage
None	378	97.4
Hypertension	6	1.5
Hypothyroidism	2	0.5
Cholecystectomy	1	0.3
Seizure disorder	1	0.3

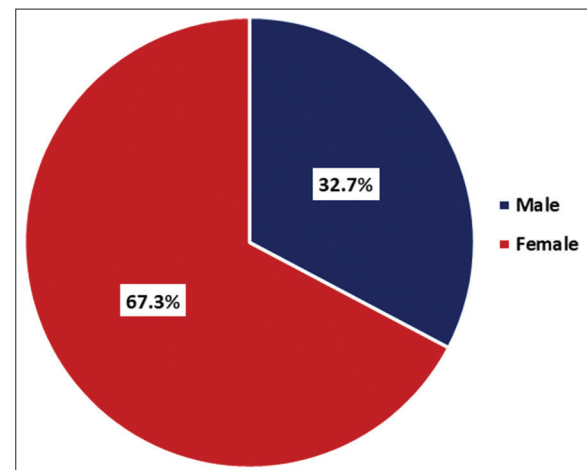


Fig. 2: Pie chart reflects the distribution of patients (n=388) as per the gender

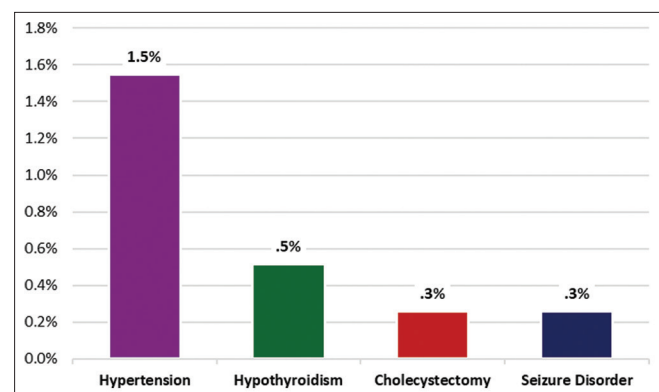


Fig. 3: Bar diagram reflects the distribution of cases (n=388) according to the past history of illness and medications

followed by lorazepam in 12.1% (n=47) of cases, alprazolam in 2.6% (n=10), clobazam in 1.5% (n=6), and chlordiazepoxide in 1.0% (n=4) of cases as per Table 4.

The analysis of the number of concomitant medicines prescribed based on the type of benzodiazepine used showed a statistically significant difference (ANOVA: $F=7.83$, $p<0.001$). Fig. 6 and Table 5 show that patients receiving alprazolam (5.80 ± 2.97) had the highest mean number of prescribed concomitant medicines, followed by those on clonazepam (5.11 ± 2.33). In contrast, patients prescribed clobazam (2.17 ± 0.98) had the lowest mean number of prescribed concomitant medicines. Those on chlordiazepoxide (3.75 ± 1.50) and lorazepam

(3.53 ± 1.61) had intermediate values. These findings suggest variations in prescribing patterns depending on the benzodiazepine used.

The association between the number of days of treatment and the type of benzodiazepine prescribed was analyzed, showing no statistically significant difference (ANOVA: $F=1.17$, $p=0.323$). The mean duration of treatment was highest for clobazam (13.67 ± 8.98 days), followed by clonazepam (11.47 ± 3.33 days) and chlordiazepoxide (11.25 ± 2.50 days). Alprazolam (11.00 ± 3.16 days) and lorazepam (10.68 ± 3.96 days) had slightly lower treatment durations. While clobazam had the longest treatment period, the differences across benzodiazepines were not statistically significant, suggesting that treatment duration was

Table 2: Distribution of patients (n=388) according to the primary complaints/diagnosis represented in absolute number and in percentage

Primary complaints/diagnosis	No of patients	Percentage
Depression with anxiety	261	67
Anxiety	72	19
Anxiety and migraine	23	6
Seizure	5	1
Alcohol withdrawal syndrome	8	2
Depression with insomnia	4	1
Bipolar disorder with anxiety	3	1
Schizophrenia with insomnia	3	1
Insomnia	5	1
Other	4	1

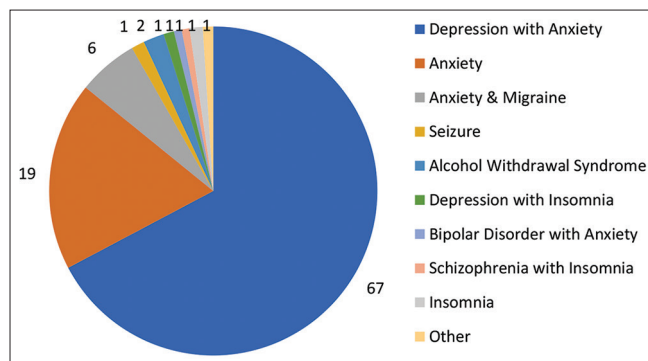


Fig. 4: Primary diagnosis of patients (n=388) in percentage receiving one medicine of benzodiazepine group

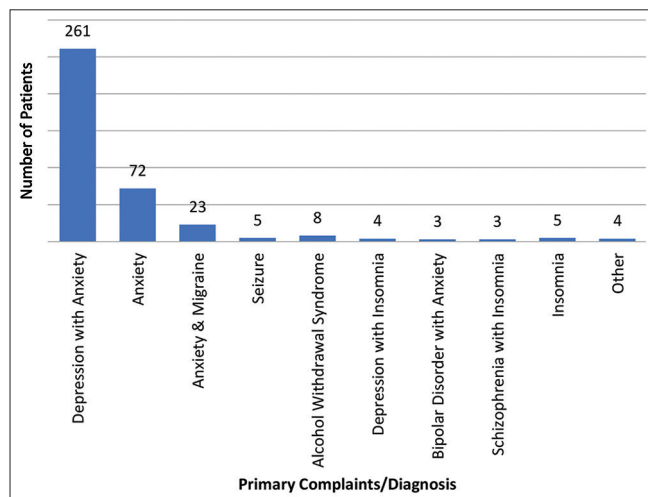


Fig 5: Primary diagnosis of patients (n=388) in absolute numbers receiving one medicine of benzodiazepine group

Table 3: Distribution of cases (n=388) according to no. of concomitant medicines prescribed

No. of concomitant medicines prescribed	No.	Percentage
One	3	0.8
Two	47	12.1
Three	105	27.1
Four	53	13.7
Five	28	7.2
More than five	152	39.2

Table 4: Distribution of cases (n=388) according to the name of the benzodiazepine prescribed

Name of the benzodiazepine	No.	Percentage
Alprazolam	10	2.6
Chlordiazepoxide	4	1.0
Clobazam	6	1.5
Clonazepam	321	82.7
Lorazepam	47	12.1

Table 5: Association of no. of prescribed concomitant drugs with the name of the benzodiazepine used showed a statistically significant difference (ANOVA: $F=7.83$, $p<0.001$)

Name of the benzodiazepine	No. of drugs prescribed	
	Mean	SD
Alprazolam	5.80	2.97
Chlordiazepoxide	3.75	1.50
Clobazam	2.17	0.98
Clonazepam	5.11	2.33
Lorazepam	3.53	1.61
ANOVA	$F=7.83$, $p<0.001$	

ANOVA: Analysis of variance, SD: Standard deviation

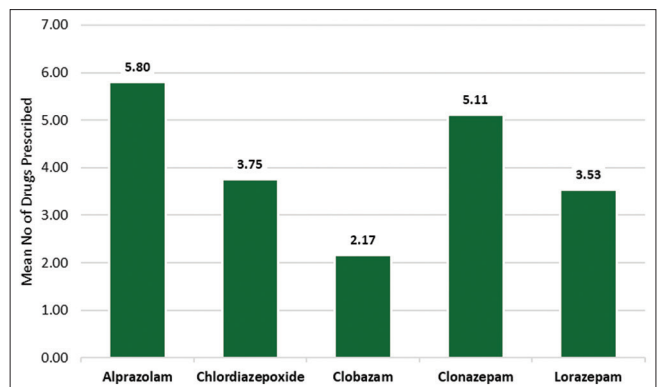


Fig. 6: Association of no. of prescribed concomitant drugs with the name of the benzodiazepine used showed a statistically significant difference (analysis of variance: $F=7.83$, $p<0.001$)

Table 6: ATC/DDD classification with calculated DID, PDD values of prescribed benzodiazepine, and PDD/DDD ratio

Drug	ATC code	DDD (mg)	DID (mg)	PDD (mg)	PDD/DDD
Alprazolam	N05BA12	1.00	0.0003	0.43	0.425
Chlordiazepoxide	N05BA02	30.00	0.0097	12.75	0.425
Clobazam	N05BA09	20.00	0.0064	15.83	0.792
Clonazepam	N03AE01	8.00	0.0026	0.47	0.059
Lorazepam	N05BA06	2.50	0.0008	1.78	0.713

ATC/DDD: Anatomical therapeutic chemical/defined daily dose, PDD: Prescribed daily dose

relatively consistent regardless of the specific medicine prescribed, as reflected in Fig. 7.

The ATC/DDD classification system provides a standardized method for evaluating drug utilization. The DDD represents the assumed average maintenance dose per day for a medicine used for its main indication in adults. The Drug Utilization Index, expressed as the DDD/1,000 inhabitants per day (DID), helps assess population-level drug consumption. In addition, the PDD reflects the actual prescribed dose, and the PDD/DDD ratio indicates the extent of deviation from the standard DDD.

In the analysis of prescribed benzodiazepines, the PDD/DDD ratio varied among different benzodiazepines. Table 6 shows that alprazolam (ATC code N05BA12) had a DDD of 1.00 mg, a DID of 0.0003 mg, and a PDD of 0.43 mg, resulting in a PDD/DDD ratio of 0.425. Chlordiazepoxide (N05BA02) had a DDD of 30.00 mg, a DID of 0.0097 mg, and a PDD of 12.75 mg, yielding a PDD/DDD ratio of 0.425. Clobazam (N05BA09) showed a relatively higher PDD/DDD ratio of 0.792, with a DDD of 20.00 mg, DID of 0.0064 mg, and PDD of 15.83 mg. Clonazepam (N03AE01) exhibited a notably low PDD/DDD ratio of 0.059; its DDD was 8.00 mg, DID was 0.0026 mg, and PDD was only 0.47 mg. Lorazepam (N05BA06) had a DDD of 2.50 mg, DID of 0.0008 mg, and PDD of 1.78 mg, leading to a PDD/DDD ratio of 0.713. This analysis is crucial for evaluating drug utilization patterns and ensuring optimal therapeutic dosing in clinical practice.

DISCUSSION

Benzodiazepines are the most commonly prescribed medicines for psychiatric illnesses. Depending upon the clinical diagnosis, they are prescribed either for short-term periods in the management of acute psychiatric illnesses or for long-term periods in the management of chronic psychiatric illnesses.

In this study, the proportion of females among the total population was more than the males, which may be due to the increased prevalence of anxiety and mood-related disorders in females. This finding was also present in other studies done in the past [4]. In our study, the most common comorbidity reported by the patients was hypertension, followed by hypothyroidism, which is similar to previously done studies [4].

In the present study, the mean number of prescribed concomitant medicines with benzodiazepines used for the study participants was less than the prescribed concomitant medicines (8.56±1.93) in the study done by Uddin *et al.* The number of concomitant medicines in a prescription can provide an opportunity for auditing the prescription. More number of prescribed medicines in prescription can have a negative impact, as far as patients are concerned, in terms of cost-escalation, poor compliance, and drug-drug interactions leading to adverse effects. This also reflects the clinician's attitude, knowledge, and expertise in cost-effective, compliant, and safe prescribing of medicines.

In this study, clonazepam and lorazepam were the most prescribed medicines of the benzodiazepine group, which is similar to other studies done in India; [8] however, a study done by Kurko *et al.* in Finland has reported midazolam and alprazolam as most prescribed medicines of benzodiazepines group. In our study, clonazepam was used for most of the study participants; however, the risk of prolonged use was

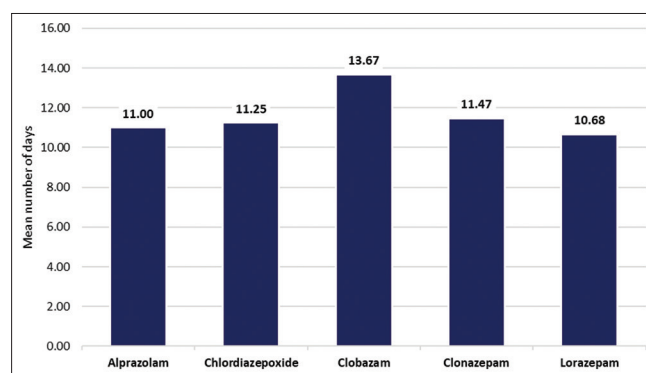


Fig. 7: Association of no of days of treatment with name of the benzodiazepine shows no statistically significant difference (analysis of variance: F=1.17, p=0.323)

lower in this study, which can be attributed to its lower dose being used resulting in a lesser probability of development of tolerance and dependence. Clonazepam can cause dependence more rapidly owing to its pharmacokinetic parameters, such as high potency and intermediate elimination of half-life. This warrants being more judicious while using clonazepam and preferring to use it in low doses and for shorter duration [9].

Our study is in alignment with various studies done in the past across the globe and has reflected that anxiety and insomnia are the most frequent indications for benzodiazepine use [10]. In the present study, all the benzodiazepines used have an intermediate onset of action, which is in agreement with similar studies done in the past [10].

CONCLUSION

Rationale prescribing of benzodiazepines can play a very crucial role in patients suffering from various mental illnesses and the outcome of the treatment. This study provides insight into the prescription pattern of benzodiazepines. Moving ahead, further research is warranted targeting a specific benzodiazepine medicine for its approved indication. Moreover, multicentric prospective studies with larger sample sizes are the need of the hour to formulate a guideline or policy regarding the usage of benzodiazepines at the national level. Considering the risk associated, regular monitoring and drug utilization studies should be done frequently with benzodiazepines and its impact on patient health and quality of life.

Limitations of the study

The limitation of our study was that we did not monitor the compliance of the patients with the prescribed drugs, and along with this, we could not evaluate the indicators reflecting patient care.

AUTHOR'S CONTRIBUTIONS

All authors participated in the research design. Dr Ambu Pandey was involved in patient selection and enrolment. Dr Shashank Shekhar Mishra was involved in data collection. Dr Jayant Rai was involved in data analyses, result interpretation, and manuscript writing. Dr Jamal Haider has done the final editing of the manuscript.

CONFLICTS OF INTERESTS

All the authors declare that they do not have any conflicts of interest in this study.

FUNDING

NIL.

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