

Medications for Anxiety: A Drug utilization study in Psychiatry Inpatients from a Tertiary Care Centre of Western Nepal

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Abstract

Background

Anxiety is the most widespread psychiatric disorder and generalized anxiety disorder is the most common disease seen in the primary care setting. Currently there are a number of anxiolytic drugs commercially available in the market for treatment of these disorders such as Benzodiazepines like Diazepam, Chlordiazepoxide, Alprazolam, Betablockers like Propranolol and H1 Antihistaminics like Hydroxyzine. Some of the newer anxiolytics like Buspirone in Azapirone group is marketed as better anxiolytic drug than the traditional drugs. Buspirone is promoted as a better drug for anxiety, as it does not cause any sedation, tolerance or physical dependence. A need for study further increases as there is no sufficient data on utilization pattern of anxiolytics on Nepalese

population. This is the first study done in the utilization pattern of anxiolytic drugs in inpatient in Nepal.

Methods

This is an observational study undertaken between 1st October 2009 and 31st March 2010 at the Psychiatric inpatient Department of Manipal Teaching Hospital. The prescribing pattern of Anxiolytic drugs was measured. Out of a total of 240 cases who were admitted to psychiatry inpatient ward, 38 cases have received Anxiolytic drugs. Those who were critically ill with anxiety were included in the study.

Results

Out of 240 cases who were admitted to psychiatry inpatient, 130 were male patients (54.2%), 95% CI [47.9,60.5] and the rest were female patients (45.8%), CI [39.5,52.1]. In 38 cases of anxiety, the age of the patient <40 years 89.5% and >40 years 10.5%. Anxiety was more common in females 71.1% than in males 28.9%. 68.4% of the patients were unemployed whereas only 31.6% of the patients were employed. 78.9% of the drugs were prescribed by trade name. Among the anxiolytics, the commonest drug prescribed was Alprazolam (50%), followed by Clonazepam (31.6%), Chlordiazepoxide (15.8%) and Lorazepam (2.6%).

Conclusion

Utilization patterns of drugs for anxiolytics were according

to treatment guidelines and suggested a trend towards the use of shorter acting Benzodiazepines such as Alprazolam. Continuous and prolonged use of longer acting Benzodiazepines has resulted in dependence and may have withdrawal symptoms when the dosage of these drugs is reduced or treatment is stopped.

Keywords: Anxiolytics, Psychiatry, Drug utilization study, Inpatients

Background

Drug utilization study is one of the fundamental watchtowers of promoting rational use of medicine for treatment of various diseases, surveying the field of healthcare and leading to a greater understanding of the development that underlies it¹. Anxiety is the most widespread psychiatric disorder and generalized anxiety disorder is the most common disease seen in the primary care setting^{2,3}. Anxiety is an unpleasant sensation characterized by apprehension, tension and fear of unknown which can develop in a normal person e.g. before an exam. Anxiety can be classified as two types, namely general anxiety (when anxiety is persistent) and episodic anxiety like phobia and panic disorder. In Panic disorder, a patient remains in a state of anxiety without any adequate cause, lasting for few minutes, characterized by palpitation, fear of unknown, sweating, dyspnea, etc. Phobia is an abnormal fear, triggered by a single stimulus, set of stimuli, which are predictable and normally cause no particular concern to others. Phobia is classified into following types like agoraphobia, claustrophobia, social phobia, simple phobia etc.

According to a literature survey done in August 2008 by Jonathan R. T et al for the period 1987–2009, anxiolytic drug groups benzodiazepines, azapirones, antihistamines, antidepressants, alpha-2-delta ligands, antipsychotics, and named drugs buspirone, venlafaxine, duloxetine, fluoxetine, escitalopram, olanzapine, paroxetine, pregabalin, quetiapine and risperidone, in addition to psychological therapies and cognitive-behavioral therapy, are commonly used treatment modalities⁴.

According to a six month prevalence rate reported in a World Health Organization (WHO) study in 14 countries including US, about 8% of patients come to a primary care with generalized anxiety disorder⁵. According to the European Study of the prevalence of Mental Disorders prevalence of anxiety is only 2.8%⁶.

Most of the studies that have been undertaken in Nepal are about the prevalence of mental illness. Only one study has been undertaken in 2001 in outpatient department of Psychiatry in Western Nepal, in which it was shown that 71.3% of the drugs were prescribed by the brand names. The frequency of use of antidepressants were 45.94%, anxiolytics 19.41%, antipsychotics 8.6% and antimanics 1.96%⁷.

Currently there are a number of anxiolytic drugs

commercially available in the market for treatment of mental disorders including Benzodiazepines like Diazepam, Chlordiazepoxide, Alprazolam, Betablockers like Propranolol and H1 Antihistaminics like Hydroxyzine. Some of the newer anxiolytics like Buspirone in Azapirone group is marketed as better anxiolytic drug than the traditional drugs. Buspirone is promoted as a better drug for anxiety, as it does not cause any sedation, does not produce any tolerance or physical dependence.

This is the first study done in the utilization pattern of anxiolytic drugs in inpatients in Nepal. By carrying out this study, one is expected to get an idea regarding clinician's choice and patient's tolerability of anxiolytic drugs. There is no sufficient data on utilization pattern of anxiolytics on Nepalese population, such studies are increasingly relevant. The main objective of the study is to find the commonest anxiolytic drug prescribed in a tertiary care centre with severe form of anxiety in hospitalized patients.

Material and Methods

Study design and the participants

A Prospective observational cross sectional study was done at Manipal Teaching Hospital, Pokhara, Nepal. It was chosen for the study because Manipal teaching hospital is a tertiary care hospital in Western Nepal and it was expected that all the critically ill psychiatric cases with anxiety will report to this hospital from Western Nepal.

Data collection

The present study was undertaken between 1st October 2009 and 31st March 2010, at Manipal Teaching hospital, Psychiatric inpatient department, at the bed side after interviewing with them. The prescribing pattern of anxiolytic drugs was measured. The data was analyzed with respect to specific factors, using following indication: Classification based on (ATC) Anatomical Therapeutic Chemical Classification, using the data on prescription, General parameters like Age (<40 years and >40years), Sex (male and female), Occupation (Housewife, teacher, labourer, shopkeeper, student, farmer, retired and others), Religion (Hindu, Christian, Muslim), Ethnicity (Brahmin, Chettri, newar, dalit and others), Employment (employed and unemployed), Monthly Income (<10000/month and >10000/month, Treatment (Drug monotherapy and drug and psychotherapy, Based on essential drug list (essential or non essential), Trade/Generic, Commonest drug were used. In types of treatment anxiolytic drugs and combination of drugs (Anxiolytics with fluoxetine) were used.

The Anatomical Therapeutic Chemical (ATC Code)⁹

Generic Name	ATC Code
Chlordiazepoxide	N05BA02
Lorazepam	N05BA06
Alprazolam	N05BA12
Clonazepam	NO3AE01
Fluoxetine	NO6ABO3

Inclusion criteria

All the patients admitted in psychiatric inpatient department with anxiety from October 2009 to March 2010 were included in the study. 38 cases had received Anxiolytic drugs and those who were seriously ill with anxiety were included in the study.

Exclusion criteria

Out of 240 cases who were admitted in the Psychiatry inpatients only 202 cases were excluded from the study because we wanted to find the drug utilization pattern of Anxiolytics drugs only. Other cases of Schizophrenia, Depression, Mania, Bipolar disorder, Substance abuse, suicidal tendencies and mental retardation were excluded from the study. All the out patients were also excluded from the study as we wanted to find the drug utilization study in those patients who are critically ill with anxiety for which hospitalization is required.

Sample size calculation

For 95% confidence interval and, significance level $\alpha = 5\%$, $P = 90\%$, $Q = 10\%$, allowable error = 11%, required sample size was 35. $P =$ percentage of Anxiolytics drugs used for the treatment of anxiety⁸.

Outcome Variables

Outcome variables were Treatment (Drug monotherapy, drug and psychotherapy), types of treatment (Anxiolytics, combined therapy), and essential drug list of Nepal (essential and nonessential drugs).

Explanatory variables

The demographic and psychiatric disorders were defined at individual level. Factors at individual level were Age (<40 years and >40 years), gender (male and female), monthly income <10000/month and >10000/month), employment of the patient (employed and unemployed).

Ethical committee approval

Preceding the study, ethical committee approval was taken from the ethical committee.

Data management and statistical analysis

Descriptive statistics and testing of hypothesis were used for the analysis. The data collected was analyzed using Excel 2003, R 2.8.0 Statistical Package for the Social Sciences (SPSS) for Windows Version 16.0 (SPSS Inc; Chicago, IL, USA) and EPI Info 3.5.1 Windows Version. The Z test was used to examine the difference between different variables and strength of the relationship with logistic regression. We calculated odds ratios (OR) and their 95% confidence intervals (95% CI). $p < 0.05$ is considered as statistically significant.

Results

Socio-Demographic Details

Our study showed that 130 inpatients were male (54.2%), 95% CI [47.9, 60.5] and the rest were female patients

(45.8%), 95% CI [39.5, 52.1]. In case of 38 cases of anxiety, 89.5% of the patients were less than 40 years of age and 10.5% were older than 40 years. Anxiety was more common in females 71.1% than in males 28.9%. 86.8% of the patients had a monthly income of less than Nepali Rupees 10000/- per month and 13.2% earned more than 10000/- per month. 68.4% of the patients were unemployed whereas only 31.6% of the patients were employed with anxiety. 97.4% of the patients were Hindus and Christians were only 2.6%. According to the ethnicity 36.8% were Brahmin and Chettri 31.6% followed by Dalit 23.7%, Newar 5.3% and others 2.6%. 39.5% of the cases were housewives followed by students 21.1% and then teachers 15.8%.

Table 1: Cross tabulation between psychiatric disorders in inpatients and Gender of the patients

Psychiatric disorders	Male	Female	Total	P Value
Schizophrenia	57 (65.5) [55.5, 75.5]	30 (34.5) [24.5, 44.5]	87 (36.3) [30.2, 42.3]	0.0001†
Depression	17 (44.7) [28.9, 60.5]	21(55.3) [39.5, 71.1]	38(15.8) [11.2, 20.5]	0.356×
Mania	5(55.6) [23.1, 88.0]	4(44.4) [12.0, 76.9]	9(3.8) [1.3, 6.2]	0.635×
Bipolar	11(55.0) [33.2, 76.8]	9 (45.0) [23.2, 66.8]	20(8.3) [4.8, 11.8]	0.525×
Anxiety	11(28.9) [14.5, 43.4]	27(71.1) [56.6, 85.5]	38(15.8) [11.2, 20.5]	0.0001†
Others	29(60.4) [46.6, 74.3]	19(39.6) [25.7, 53.4]	48(20.0) [14.9, 25.1]	0.037*
Total	130 (54.2) [47.9, 60.5]	110 (45.8) [39.5, 52.1]	240	0.067×

† $p < 0.01$, statistically significant

* $p < 0.05$, statistically significant

× $p > 0.05$, statistically not significant

Psychiatric disorders

Table 1 shows that out of 240 cases admitted to the psychiatry ward, the most common psychiatric disorder was Schizophrenia 36.3% and other diseases like substance abuse, behavioral disturbances, mental retardation and suicidal tendencies constituted 20%, followed by Depression and anxiety disorders 15.8%. Mania 3.8% and Bipolar disorders 8.3% were the least in number. There were 65.5% male and 34.5% female patients, 95% CI [55.5, 75.5 and 24.5, 44.5 respectively] suffering from Schizophrenia, which was found to be highly statistically significant ($P = 0.0001$). In Depression, out of 38 cases, male and female patients were 44.7% and 55.3% respectively, 95% CI [28.9, 60.5 and 39.5, 71.1]. In case of Mania, in 9 cases male and female patients were 55.6% and 45.4% respectively, 95% CI [23.1, 88.0 and 12.0, 76.9]. In case of Bipolar disorders out of 20 cases, male and female patients were 55% and 45% respectively 95% CI [33.2, 76.8 and 23.2, 66.8]. In patients with anxiety out of 38 cases, the percentage of male and female patients were 28.9% and 71.1%, 95% CI [14.5, 43.4 and 56.6, 85.5] which was found to be highly statistically significant ($P = 0.0001$). In case of other psychiatric cases,

male and female patients were 60.4% and 39.6% respectively and 95% CI [46.6, 74.3 and 25.7, 53.4].

Figure 1 depicts that as per as occupation of the patient is concerned housewives (39.5%) 95% CI [23.9, 55.0], suffer more from anxiety which is followed by students (21.1%) 95% CI [8.1,34.0],and teachers(15.8%) 95% CI [4.2,27.4], laborer (5.3%) 95% CI[0.12.4],farmer (5.3%)95% CI [0,12.4], retired (2.6%) 95% CI[0,7.7], shopkeeper (2.6%) 95% CI[0,7.7] and others (7.9%)(95% CI [0,6.5].

Figure 1: Occupations of patients suffering from anxiety

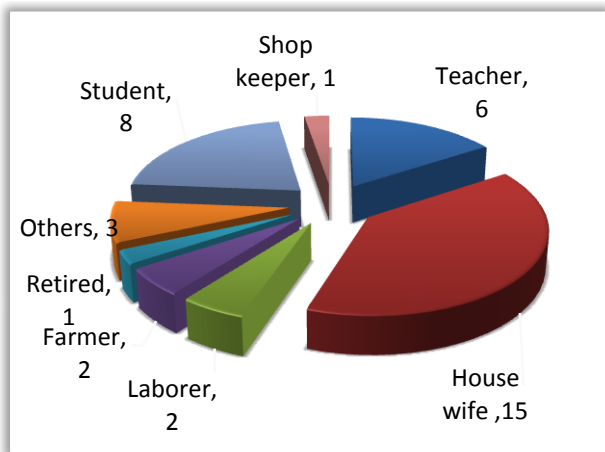


Table2: Cross tabulation between Socio demographic factors and Treatment, and Types of treatment

Socio demographic factors		Treatment		Types of treatment	
		Drug Monotherapy	Drug and Psychotherapy	Anxiolytics	Combined
Age	< 40 yrs	17 (89.5)	17 (89.5)	28 (90.3)	6 (85.7)
	>40 yrs	2(10.5)	2(10.5)	3(9.7)	1 (14.3)
	Total	19(100)	19(100)	31(100)	7(100)
	P Value	0.0001†	0.0001†	0.0001†	0.0001†
Gender	Male	4(21.1)	7(36.8)	7 (22.6)	4 (57.1)
	Female	15(78.9)	12(63.2)	24(77.4)	3(42.9)
	Total	19(100)	19(100)	31(100)	7(100)
	P Value	0.0001†	0.09*	0.0001†	0.589*
Employment	Employed	5(26.3)	7(36.8)	8(25.8)	4(57.1)
	Un employed	14(73.7)	12(63.2)	23(74.2)	3(42.9)
	Total	19(100)	19(100)	31(100)	7(100)
	P Value	0.0001†	0.0001†	0.0001†	0.08*
Monthly Income	< 10000 /month	17(89.5)	16(84.2)	28(90.3)	5(71.4)
	>10000 /month	2(10.5)	3(15.8)	3(9.7)	2(28.6)
	Total	19(100)	19(100)	31(100)	7(100)
	P Value	0.0001†	0.09*	0.0001†	0.589*

† p<0.01, statistically significant
 * p<0.05, statistically significant
 × p>0.05, statistically not significant

Table 2 reveals cross tabulation between Sociodemographic factors and treatment and type of treatment. If the age of the patient is <40 years, patients receiving drug monotherapy 89.5%, drug and psychotherapy 89.5%, Anxiolytics 90.3%, Combined therapy 85.7% was found to be highly statistically significant (P=0.0001). 78.9% female patient received drug monotherapy and 77.4% of female patient received Anxiolytics which was found to be highly statistically significant (P=0.0001). If the patient is unemployed 73.7% patient received drug monotherapy, 63.2% received drug and psychotherapy, 74.2% received Anxiolytics (P=0.0001). If the monthly income is <10000, 89.5% received drug monotherapy only and 90.3% received Anxiolytics (P =0.0001).

Table 3: Logistic regression table of Essential drug list and socio demographic factors

Socio demographic factors		Essential Drug List		Odds ratio and Confidence interval
		Non essential	Essential	
Age	< 40 yrs	17(94.4)	17 (85)	2.811(0.211,37.393) ×
	>40 yrs	1(5.6)	3 (15)	
	Total	18 (100)	20(100)	
Gender	Male	4 (20)	7(38.9)	2.568(0.582,11.333) ×
	Female	16(80)	11 (28.9)	
	Total	20(100)	18(100)	
Employment	Employed	6(33.3)	6(30)	0.948(0.225,3.998) ×
	Unemployed	12(66.7)	14(70)	
	Total	18(100)	20(100)	
Monthly Income	< 10000	16(88.9)	17(85)	1.148(0.129,10.205) ×
	>10000	2(11.1)	3(15)	
	Total	18(100)	20(100)	

× p>0.05, statistically not significant

Table 3 depicts that doctors have a 1.148 times more tendency of prescribing essential drug to a patient who have monthly income more than 10000 compared to monthly income <10000 and incase of age group >40 year 2.811 times more compared to <40 years, employed patient 0.948 times and to female patients 2.568 times more than male patients.

Figure 2: Most common Anxiolytics prescribed

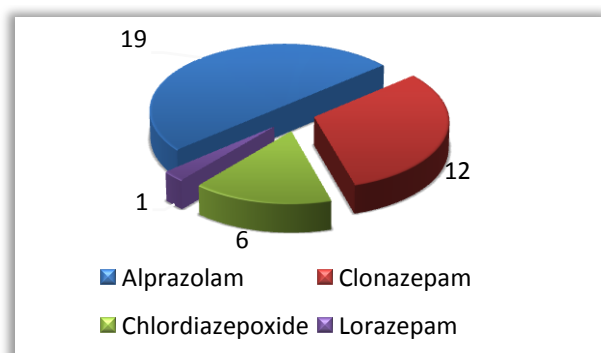


Figure 2 depicts the most common anxiolytics prescribed were alprazolam 19 (50) and clonazepam 12 (31.6) followed by chlorthalidone 6(15.8) and lorazepam 1(2.6).

Table 4: Cross tabulation between Socio demographic factors and Anxiolytic drugs prescribed

Socio demographic factors	Drugs Prescribed				
	Alprazolam	Clonazepam	Chlorthalidone	Lorazepam	
Age	< 40 yrs	15(78.9)	12(100)	6(100)	1(100)
	>40 yrs	4(21.1)	0(0)	0(0)	0(0)
	Total	19(100)	12(100)	6(100)	1(100)
	P Value	0.0001†	-	-	-
Gender	Male	4(21.1)	3(25)	3(50)	1(100)
	Female	15(78.9)	9(75)	3(50)	0(0)
	Total	19(100)	12(100)	6(100)	1(100)
	P Value	0.0001†	0.0004†	1 ^x	-
Employment	Employed	7(36.8)	3(25)	2(33.3)	0(0)
	Un employed	12(63.2)	9(75)	4(66.7)	1(100)
	Total	18(100)	12(100)	6(100)	1(100)
	P Value	0.09 ^x	0.0004†	0.221 ^x	-
Monthly Income	< 10000 /month	14(73.7)	12(100)	6(100)	1(100)
	>10000 /month	5(26.3)	0(0)	0(0)	0(0)
	Total	19(100)	12(100)	6(100)	1(100)
	P Value	0.0001†	-	-	-

† p<0.01, statistically significant
 x p>0.05, statistically not significant
 - P value cannot calculate

Table 4 reveals that if the age of the patient is <40 years 78.9% of the patients used alprazolam, if the gender of the patient is female 78.9% of the patients used alprazolam and if the monthly income of the patient is <10000 Rs/month 73.3% of the patients used Alprazolam which was found to be highly statistically significant in all the cases (P=0.0001).

Discussion

Drug Utilization Research

Drug utilization research is defined as research on marketing, distribution, prescription and use of drugs in a society with a special emphasis on the resulting medical, social and economic consequences and has the principle aim of facilitating the essential and rationale use of the drugs. Every patient always wants a good prescription ,well documented, with an optimal dose and drugs with acceptable and as few side effects as possible at an affordable price, with correct information. Drug utilization research provides a baseline reference point about the effect of various interventions on prescribing about the drugs¹⁰. Drug utilization studies in Psychiatric disorders are few in number in Nepal. We could lay our hands only on one study done in 2001 by P. Ravishankar and S. Roy in outpatient department⁷. Our study was done in an inpatient setting because it is easy to follow up the patients. Psychiatric cases with anxiety that were seriously ill and require inpatient admission were taken into consideration.

Psychiatric diseases

Out of 240 cases who were admitted to the psychiatric inpatient ward from October 2009 to March 2010, Schizophrenia cases were predominant 36.3% out of which 65.5% were males and 34.5% were females. This is followed by Other Psychiatric disorders like substance abuse, behavioral disturbances, suicidal tendencies and mental retardation 20%, in which 60.4% patients were male and 29.6% were females. This is followed by Depression 15.8%, in which 55.3% of the patients were females and 44.7% were male patients and anxiety 15.8%. In this disease 71.1% of the patients were females and males were only 28.9%. Bipolar disorders 8.3% and Mania 3.8% were the lowest. Our findings are different from a similar study done in Nepal in which it was shown that the prevalence of mental illness were estimated about 25% of the total population of Nepal among which 1-2% cases were Psychosis, Neurosis 10%, Depression 4-6%, Mental retardation 3-5%, Alcohol abuse disorder 3-5%, Narcotic and other substance use disorders 0.5%¹¹. In another study done in 2000 in Jiri, Nepal showed that out of 653 patients 11.08% had somatization disorder, Generalized anxiety disorder 3.5%, Depression 3.1%, Mania 3.6%, Schizophrenia 1.4% and Antisocial personality disorder 0.2%¹².

Socio-Demographic Details and Anxiety

Out of 38 cases of anxiety, 71.1% of the patients were females and only 28.9 % were males. This finding is similar to a study done by Lader MH et al in Australia which also showed that psychiatric disorder is more common in females¹³.

Maximum cases of anxiety were below 40 years of age 89.5% and only 11.5% were above 40 years of age, which is also similar to a study done by Raut P in South India, which revealed that psychiatric illness occurs more in patients below 40 years of age¹⁴. A study done by Cheng Shannon J et al, showed significant increase in antipsychotics prescribing for youths, mainly because of growing use of second generation agents for non psychiatric illness¹⁵.

As far as religion is concerned, anxiety cases were more common in Hindus 97.4%, followed by Christian 2.6%. Among the ethnic groups, Brahmins 36.8%, Chettri 31.6% were the most prominent anxiety cases followed by Dalit 23.7%, Newar 5.3% and others 2.6%. Anxiety was more commonly seen in unemployed population 68.4%. As far as the monthly income is concerned, majority of the cases earned less than Rs 10000 NPR/month (86.8%).This finding is similar to a study done in Sweden in 2006, in which it was concluded that psychotropic drug utilization was higher among individuals with low income and unmarried population¹⁶.

Anxiety was most common in housewives (39.5%), students (21.1%), followed by teachers (15.8%). Qualitative research done in housewives with the personal interview tool revealed that this is due to their husbands being in foreign countries for employment, or them deserting their family in

the village to migrate to bigger cities of Nepal, India or foreign countries.

Pharmacotherapy of Anxiety

As far as the drug utilization is concerned 50% of the patients received drug monotherapy alone which were equal to that of drug therapy and psychotherapy. None of the cases were treated by psychotherapy alone.

As far as the Trade and Generic is concerned, 78.9% of the anxiolytics were prescribed by Trade name where only 21.1% were prescribed by Generic name. Our finding is similar to a study done by Ravishankar P.R et al in 2001 on psychotropic drugs where it was found that 71.3% of the drugs were prescribed by Trade names⁷.

The use of Essential drug list was almost 52.6% as compared to nonessential drug list 47.4%. In another study it showed that 29.48% of the drugs prescribed were from essential drug list of Nepal⁷. According to the essential drug list of Nepal, among the anxiolytic drugs only Alprazolam and Chlordiazepoxide are included¹⁷.

In the type of treatment given for anxiety, anxiolytics were given in 81.6% of the cases, whereas a combination of anxiolytics and antidepressants like Fluoxetine (Selective serotonin reuptake inhibitors) were given in 19.4% of the cases. Among all the cases of anxiety Benzodiazepine group of drugs were used. In none of the cases of anxiety other group of drugs like H1 antihistaminics, β blockers like propranolol or Azapirones like Buspirone were used. Our finding is similar to the other studies which revealed that in Benzodiazepines were the commonest psychotropic drugs prescribed¹⁸.

Among the anxiolytics the commonest drug was Alprazolam 50%, followed by Clonazepam 31.6%, Chlordiazepoxide 15.8% and Lorazepam 2.6%, suggesting a trend towards the use of shorter acting Benzodiazepines, as it is seen that continuous and prolonged use of longer acting Benzodiazepines has resulted in dependence and may have withdrawal symptoms when the dosage of these drugs are reduced or treatment is stopped¹⁹.

Antidepressants and Benzodiazepines are the most commonly prescribed psychotropic drugs. It is difficult to know whether these drugs are being inappropriately prescribed. Published evidence merely tells us that antidepressants are effective in moderate and severe depressive illness²⁰. Benzodiazepines are extremely effective in promoting sleep and relieving anxiety in short term²¹.

Conclusion

Utilization patterns of drugs for Anxiolytics were according to treatment guidelines i.e Alprazolam, suggesting a trend towards the use of shorter acting Benzodiazepines as it is seen that continuous and prolonged use of longer acting Benzodiazepines has resulted in dependence and may have withdrawal symptoms when the dosage of these drugs is reduced or treatment is stopped.

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Authors contributions

IB designed the study, interpreted the data, drafted the manuscript, and revised it. BR envisages the study with IB, acquired the data, conducted the data analysis, interpreted the data, and revised the manuscript. KSS revised the manuscript; BS participated in statistical analysis, interpreted the data, and revised the manuscript. SA and IB2 interpreted the data and critically revised the manuscript. All authors approved the final manuscript.

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