

## Benzodiazepine use in medical out-patient clinics: a study from a developing country

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### Abstract

**Objective:** To estimate the prevalence of Benzodiazepine use in the outpatient setting of general medicine clinics at a single tertiary care centre.

**Methods:** The prospective prevalence study was conducted in the outpatient setting of Internal Medicine Clinics at Aga Khan University Hospital, Karachi, from November to December 2009. All subjects were interviewed after informed consent and variables were recorded on a specially-designed proforma. Apart from basic demographics and comorbid conditions, duration, frequency and route of benzodiazepine use, as well as the reason and who initiated it was noted. Chi-square test and t test was applied to see the association of socio demographic or clinical factors with the use of benzodiazepine.

**Results:** Of the 355 patients, 129 (36.33%) reported using the drug. The majority (n=86; 24.2%) were taking it on a daily basis. The highest numbers of patients using the drug were suffering from cardiovascular problems, 32 (25%) followed by 22 (17%) from endocrinology. Diazepam equivalent dose was around 7.04±4, with an inter-quartile range of 3-96 weeks. Alprazolam (9%) was the most frequently prescribed Benzodiazepine.

**Conclusion:** Benzodiazepine use is alarmingly high in the outpatient clinics of General Internal Medicine Department. There is no implementation of law to prevent its hazardous sale. In this regard all concerned should work collectively for awareness and irrational drug sale and use.

**Keywords:** Benzodiazepine, Medical out-patient, Prevalence, Dependence, Drug use, Pakistan. (JPMA 63: 717; 2013)

### Introduction

Anxiety and insomnia are common clinical presentations for centuries. Efforts have been made by healers of each era to lower human sufferings regarding these ailments. This quest has led to different classes of medications that surfaced in recent times such as bromides in 1920, followed by Barbiturates in 1940. Benzodiazepine (BDZ) was a major breakthrough in the form of Chlordiazepoxide in 1957. It gained popularity as higher doses were not as toxic as its predecessors. This became the selling point, but in the late 1970s and early 1980s attention was focussed towards iatrogenic effects of BDZ, i.e. dependence.<sup>1</sup>

In the fifth decade of its use, BDZ is still the widely and most frequently prescribed drug. Prevalence estimates from National Epidemiologic Survey on Alcohol and related conditions in USA suggest 0.16 % and 0.13 % of sedative and tranquiliser use respectively in 2001-02.<sup>1</sup> In Canada, frequency of hypnotic and similar sedative hypnotic use was found around 3.4%.<sup>2</sup> Women and less

educated people were using it more. In France and Italy, BDZ use came around 7.5% and 8.6% respectively.<sup>2,3</sup> Comparing estimates of US and Canada with European countries like France gives one some clue to establish a global picture.

In in-patient setting, BDZs are frequently prescribed but without proper documentation.<sup>4</sup> This is why taking the scenario of pharmacy system or point prevalence would give a clue towards the specialty as reported in a study<sup>5</sup> which looked into prescription rates of BDZ among different specialties and reported neurology as the highest prescribing specialty (35.8%) followed by orthopaedics (26%).<sup>5</sup> A similar study from Pakistan reported point prevalence of 21% of BDZ use in admitted patients.<sup>6</sup> It also reported surgical specialties using it more as compared to non-surgical specialties and short-acting Midazolam as the most commonly used one. Another cross-sectional survey estimated the prevalence of BDZ use around 30% in patients visiting out-patients clinic of different specialties.<sup>7</sup>

Long-term use of BDZ leads to dependence. Dependence has been estimated by different studies, that came as high as 45% after six months of continuous use.<sup>1,2</sup> This significant adverse effect profile raised the concern amongst the medical community. It then led to the development of

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guidelines to restrict its use for pre-anaesthesia, alcohol detoxification and short-term use for anxiety disorders.<sup>8</sup> Despite these measures, BDZs are regarded as one of the most prescribed class of medications.<sup>9</sup>

The Drug Abuse Warning Network (DAWN) reported an increasing trend in the abuse of BDZ (38%) from 1995 to 2002. In this survey, Alprazolam (Xanax®) was reported to be the highest (62%).<sup>10</sup> A recent study from Pakistan also revealed BDZ overdose (41%) as the most common method of deliberate self-harm in women more than men.<sup>11</sup>

A study from Pakistan pointed towards the prevalence of BDZ use in out-patient psychiatric clinics in two major cities of Pakistan (Karachi and Lahore) giving alarming results of 45%.<sup>12</sup> Psychiatric disorders were estimated around 15-20% in people presenting with organic disorders.<sup>13,14</sup> Medically un-explained symptoms constitute about one-third of all patients presenting to doctors. These become a part of larger group of illness, underlying stress, anxiety and depression that responds to treatment.<sup>15</sup> General Physicians (GPs) may feel overwhelmed on such psychological issues and see BDZ as the "lesser evil" in terms of consolidating doctor-patient relationship.<sup>16</sup>

It was thought of high interest and value to see BDZ use in Internal Medicine clinic. We did not come across any study examining this before from Pakistan.

The objective of the study was to assess period prevalence and patterns of BDZ use in out-patients of Internal Medicine practice at a tertiary care centre in Karachi, Pakistan.

## Subjects and Methods

The prospective prevalence study was conducted in the outpatient clinics of Internal Medicine at the Aga Khan University Hospital (AKUH), in Karachi, Pakistan. Ethical approval was obtained prior to the study. All patients of age above 18 who visited the clinic from November to December 2009 were interviewed. Mentally challenged and seriously ill patients were excluded.

The questionnaire/proforma was developed initially by experts after group discussion and also has been used previously in a study.<sup>12</sup> The survey was conducted by Medical Final Year students voluntarily. Before data collection all volunteers were trained for it. The data was collected till the sample size requirement was met. The proforma encompassed relevant demographic details like age, gender and level of education etc. The patients were asked regarding BDZ use, reason to start, duration, frequency, dosage, type and route of BDZ use. They were enquired about who prescribed it whether it be a GP, psychiatrist, self-medicated etc. All co-morbid illnesses were noted. Diazepam-equivalent doses were calculated

using Maudslaey Prescribing guidelines.<sup>17</sup>

Taking estimated prevalence of BDZ use as 30.4% at a tertiary care hospital as found in literature,<sup>7</sup> and taking precision of 5%, a minimum of 323 subjects were required, at 0.05 level of significance and 80% power. We took a total of 355 patients.

SPSS 16.0 was used for data analysis. Chi-square test was used to analyse categorical variables like city, gender, whether seen by physician or psychiatrist before, etc.; and t-test to analyse continuous variables like age. Use of BDZ was taken as dependent variable and other variables that were statistically significant ( $p < 0.05$ ) as independent variables.

## Results

The mean age of the 355 patients was  $45 \pm 17$  years. Inter-quartile range was 32-60 years. Of the total, 185(52%) were males; 268(75%) were married; and 87(24%) were single or widowed. Housewives formed the largest group 116(33%) followed by professionals 74(21%), students 44(12%) and retirees 42(11%). Majority of them ( $n=134$ ; 38%) were graduates (Table). Patients who presented to the clinic for medical evaluation were mostly suffering from both cardiovascular (CVS) 92(26%) and infectious disease etiology 92(26%) followed by endocrine-related problems 82(23%), gastrointestinal diseases 57(16%), musculoskeletal problems 46(13%), Central Nervous System (CNS) diseases 32(9%) and pulmonology 25(7%) problems, whereas genitourinary 11(3%) and haematology 01(0.3%) related illnesses were the least reported (Figure).

A total of 129(36%) patients reported current use of BDZ. Of these, 58(45%) continued the use of BDZ on their own as compared to 30(23%) of the cases where it was

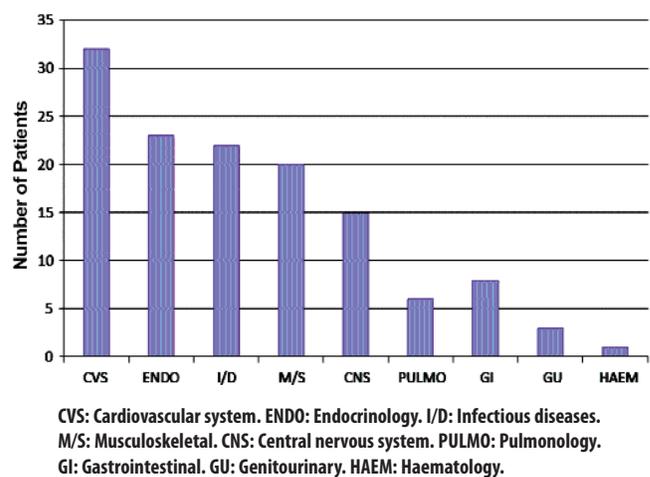


Figure: Period prevalence of benzodiazepine use by medical diagnosis.

Table: Association between socio-demographic and clinical variables and likelihood of taking benzodiazepine.

Variables	Number (%)	Taking Benzodiazepine (%)	P-value
<b>Gender (n=355)</b>			<0.169
Male	185(52)	61(47)	
Female	170(47)	68(53)	
TOTAL	355	129(100)	
<b>Marital Status(n=355)</b>			<0.002
Married	268(75.4)	101(78)	
Single/widowed	87(24.5)	28(22)	
TOTAL	355(100)	129(100)	
<b>Education</b>			<0.005
Primary and below	73(20.5)	38(29)	
Secondary	55(15)	20(15)	
Intermediate	80(22.5)	17(13)	
Graduate	134(38)	51(39)	
Postgraduate	13(4)	3(2)	
TOTAL	355(100)	129(100)	
<b>Occupation</b>			<0.001
Professional	74(21)	25(19)	
Labour	45(13)	15(12)	
Businessman	33(9)	11(8)	
Student	44(12)	4(3)	
Housewife	116(37)	51(39)	
Retired	42(12)	23(18)	
Unemployed	1(0.2)	0(0)	
Total	355(100)	129(100)	

prescribed persistently by GPs or internists. There was no gender difference in the prevalence of BDZ use. Among the single and widows 28 (22%) were on BDZ compared to 101 (78) of the married. Housewives reported using BDZ in 51 (39%) cases, becoming the largest group, followed by 23 (18%) of the retired persons, labour 15 (12%), professionals 25 (19%) and 11 (8%) business-persons. Use of BDZ was the highest in people having primary education or less 38 (29%) and graduates 51 (38%).

Disease-specific description of BDZ use pointed out some interesting results as 32 (25%) patients suffering from CVS problems were using BDZ, followed by 23 (18%) in endocrinology, 22 (17%) in infectious diseases, 20 (15%) in musculoskeletal, 15 (12%) in CNS problems, 6 (5%) in pulmonology, 8 (6%) gastrointestinal, 3 (2.3%) in genitourinary and 1 (0.7%) in haematology. Among psychiatric illnesses, generalized anxiety disorder was the only diagnosis reported by 6 (5%).

Among the users, majority (n=31; 24%) were using BDZ on a daily bases and reported insomnia and anxiety as reasons for its use. Diazepam-equivalent dose was calculated to be around  $7.04 \pm 4$ , and mean duration of use was  $93.07 \pm 203$  weeks, with an inter-quartile range of 3-96 weeks. Frequency of particular BDZ being taken was

Alprazolam (n=22; 17%), Bromazepam (n=15; 12%), Lorazepam (n=5; 4%) and Midazolam (n=3; 2%).

## Discussion

There is paucity of data from this part of the world regarding the use of BDZ in an outpatient setting of General Internal Medicine clinics. The current study reports point prevalence estimates of BDZ use in this group as well as give important demographic and relevant clinical correlates.

Prevalence of BDZ usage in our population came around 36%, which can be compared with 21% in the in-patient setting at the same institute but without discrimination of any specific specialty.<sup>6</sup> In a study done in all out-patient clinics of the same hospital gave a lifetime prevalence of BDZ at around 30%.<sup>7</sup>

A study done at psychiatry out-patient reported 45% point prevalence of BDZ use in Pakistan.<sup>13</sup> Psychiatrists are primarily responsible for prescribing and managing anxiety and insomnia issues, but our data gave a new angle, as in 85 (23%) cases it was started by an internist or a GP compared to the psychiatrists who started it in only 20 (6%) cases. Self medication in our study population came alarmingly high at 58 (16%). In Pakistan there are no strict laws to restrict the selling of BDZ as a prescription medication only. This may be the reason behind self-prescribers being the highest in number. Greater prescription rate by an internist may also be understandable from the phenomena reported in a qualitative study that GPs take BDZ as the lesser evil ["people do not die by BDZ"].<sup>17</sup>

In gender-wise description, BDZ usage was almost equally prevalent in females (68%) and males (61%). This finding is different from previous studies.<sup>13</sup> Housewives as the second largest group of BDZ users is significant because in one previous study reported that depressed housewives were at greater risk of self-harm, giving an alarming picture and also reporting that BDZ was the most commonly used option. Among the users, the majority were married, which is in contrast to high prevalence in separated and divorce population findings by one study.<sup>18</sup> This may be correlated with distress associated with the institution of marriage in Pakistan. Primary education and no education both have high prevalence of BDZ use.

Majority of the cases presented with symptoms related to infectious diseases, whereas CNS diseases were low. In system-specific description, people presented with CVS-related illnesses were the highest in taking BDZ, followed by Endocrine problems, infections-related problems and

musculoskeletal problems. The results can be compared with a study in Japan, where they focussed on in-patient pattern of BDZ prescription, giving Neurology as the highest in prescribing (35.8%), followed by cardiac surgery (35.8%), orthopedics (26.3%), general surgery (24.1%) and internal medicine (23.7%).<sup>10</sup> As our study was conducted in Medicine clinics, it was likely to have less cases related to surgical problems. High BDZ use in patients suffering from CVS problems may also be explained over Pakistan-specific prescription trend as here GP/Internist prescribes BDZ for the control of hypertension.<sup>19</sup>

Alprazolam was used the most, followed by Bromazepam, Lorazepam and Midazolam, while the rest were in much lower numbers. Differences from previous two studies at the same institution explain that in psychiatric out-patient, Clonazepam (longer duration) was the highest and in all in-patients it was Midazolam (shortest acting).<sup>6,13</sup> This is understandable as psychiatrists prescribed BDZ for anxiety and insomnia primarily compared to the Internist and surgical team for anxiety and surgical procedures.

In terms of limitations, the study was conducted at a private-sector hospital where patients have to pay from their pocket, thus limiting easy access of patients. The study sample, as such, may not be the true representative of the general population. Secondly, as this study is based on self-reporting patients, it carries a risk of under-reporting, which also limits its generalisability. A sample size of 355 patients is not enough to elicit significant aspects of this important issue and we believe that a larger sample size is needed for more relevant results.

## Conclusion

BDZ use was found to be alarmingly high. Despite established high risk of dependence associated with BDZ use, they were prescribed randomly. Self-medication trend also was an eye opener, reflecting the need to increase awareness among all stakeholders. Retirees and housewives as major groups were flagged, pointing a need to develop some drug monitoring system.

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