

The Use of Benzodiazepines in a Primary Outpatient Care Unit: The Impact of Anxiety Disorders and Depression

Uso de benzodiazepínicos em um centro de atendimento médico ambulatorial: o impacto dos transtornos ansiosos e depressivos

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RESUMO

Objetivo: verificar a prevalência de uso de benzodiazepínicos (BZD) em pacientes de serviço ambulatorial de atendimento primário à saúde e comparar a prevalência de transtornos de ansiedade e depressão entre os pacientes que relataram e negaram uso destes medicamentos. *Método:* Foram entrevistados 103 pacientes ao acaso, de ambulatório de clínica médica de um hospital universitário. O diagnóstico psiquiátrico foi realizado com o uso da Entrevista Neuropsiquiátrica Internacional Resumida, versão 4.4. *Resultados:* 43 (41,7%) dos pacientes relataram uso atual ou passado de BZD. Este grupo apresentou mais significativamente transtornos de ansiedade (χ^2 , $p=0,028$) e depressão (χ^2 , $p=0,019$), comparado ao grupo que negou uso passado ou atual de BZDs. *Conclusão:* É fundamental o reconhecimento dos transtornos de ansiedade e depressão pelos médicos responsáveis pelo atendimento primário à saúde, a fim de melhorar qualidade de vida destes pacientes e reduzir a prescrição de BZD para os mesmos.

PALAVRAS-CHAVE: ansiedade, depressão, benzodiazepinas, ambulatório hospitalar.

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ABSTRACT

Objective: To verify the prevalence of benzodiazepines (BZD) use in primary care outpatients and to compare the prevalence of anxiety and depressive disorders between those who reported and denied BZD use. *Method:* 103 randomly selected patients of an outpatient clinic of a university hospital were interviewed. Psychiatric diagnoses were assessed with the Mini-International Neuropsychiatric Interview 4.4 Version. *Results:* 43 (41.7%) patients reported past or present use of BZDs. This group presented significantly more anxiety disorders (Chi square, $p=0.028$) and depression (Chi square, $p= 0.047$), when compared to the group who denied past or present BZD use. *Conclusion:* The recognition of anxiety and depressive disorders by primary care doctors is of utmost importance, in order to improve the quality of life of these patients and reduce the prescription of these drugs.

KEYWORDS: anxiety, benzodiazepines, depression, outpatient clinics.

INTRODUCTION

The anxiety disorders and depression have some specific therapeutic interventions based in careful conducted clinical trials. The benzodiazepines (BZD) prescriptions may be an exception to this rule as although they are frequently prescribed. Some myths about the BZD utilization keep on challenging the correct and useful prescriptions of these drugs (Bueno 1980). Among the various treatments for anxiety disorders the anxiolytic and hypnotic actions of the BZD are one of the most efficacious. However, the uncorrected prescriptions of BZDs can lead to the dependence or abuse syndromes (Schweizer and Rickels 1998)

Costa e Silva (1999) pointed that the main reason for the success of the BZD was the safe profile as there was a rouge gain in the therapeutic index compared with the previous drugs for the treatment of anxiety as barbiturates and Meprobamate. Certainly this aspect influenced to an increase in prescriptions in all the fields of medicine especially in psychiatry. In the late 70's, drugs as diazepam were among the most prescribed drugs in the world for the disorders of the Central Nervous System (CNS) (Tone 2005).

According to Laranjeira and Castro (2005), an important behavior feature of the subject using a BZD is to "search for the drug". The patients use many different plans and unsafe ways to obtain a prescribed BZD what may develop a difficult

relationship with the physician, as they may feel discomfort with the patient's pressure to prescribe the BZD without a clear clinical target.

Since its introduction in the market in the sixties until nowadays the BZD have been the most prescribed group of drugs in the whole world (Soares et al. 1991; Gabarron et al. 2002). Different studies show that the majority of prescriptions come from general physicians targeting patients with somatic complain (Karniol et al. 1985). In Brazil, some very consistent data were found from 1976 to 1978. Three patterns of BZD uses were detected: the regular use (56.1%), the occasional use (38.1%) and the episodic use (4.4%) (Soares et al. 1991).

Although the BZD have a very safe profile, the restrictions to its prescriptions very been increasing due to concerns about its side effects related to depression of the CNS. Among them, the main side effects are decrease of psychomotor activity, memory deficit, paradox agitation, tolerance, dependence, and the increase of the depressive effect of other drugs including alcohol (Auchewski et al. 2004).

Frances and Miller (1998) found that 1.6% of the adult population uses BZD chronically, especially women with more than 50 years of age and with some chronic illness, mainly anxiety disorders. In Brazil it was conducted by the CEBRID (Brazilian Center of Information About Drugs) in 2001, the first House Survey on the psychotropic. It demonstrated

that 1.1% of the 8,589 subjects interviewed from 107 Brazilian cities with more than 200 thousand inhabitants fulfilled the criteria for BZD dependence (Auchewski et al. 2004).

The anxiety disorders and depression are more frequent in patients with chronic somatic illness. This association usually brings some additional difficulties for the precise diagnosis. It is usual to find some limitations in different aspects of the patient's life and the imprecisely prescription of BZD when the anxiety disorder or depression are not identified together with the chronic somatic illness (Fulop et al. 1987). Bridges e Goldberg (1985) described a classical observation that among patients with mental disorders as the central problem, 83% had a main somatic complain and 17% had a psychological complain.

A Brazilian epidemiologic study (Soares et al. 1991) observed the prevalence of BZD use in a sample of tertiary public medical unit outpatients. They evaluated 164 patients from a general physician unit (52.2%), surgical unit (20.8%), dermatology and neurology unit (20.2%), and psychiatry (6.8%). They found that excluding the psychiatry unit, 45.3% of the whole sample had used BZD (23.9%) or are using it (21.3%). Among the psychiatric outpatients it was observed that 62.2% were using BZD at the time of the survey and 31.5% had previously used BZD. In conclusion it was detected a higher prevalence of BZD use in the psychiatric population with a clear tendency for a daily and chronic pattern than all the other clinical samples studied.

In another study in the southern city of Porto Alegre (Wortmann et al. 1994), 480 inhabitants were randomly selected with an age of 18 years or more and they were interviewed in their homes in June 1991. A prevalence of 46.7% (n=224) for BZD use was found. Among men, 36.7% had use BZD at least once, while among women the proportion observed was 53.4%. This difference was statistically significant. The most used drugs were diazepam, bromazepam, lorazepam, and oxazepam, respectively. The authors were surprised that almost 50% of the studied population had used BZD at least once during its life.

In the same way, Horta et al. (1994) registered all the medical visits and their prescriptions in a 12-month period. The authors analyzed the BZD prescriptions in 3,368 medical visits for patients. After the acetylsalicylic acid and hydrochlorothiazide, the BZD was the third more prescribed drug for men and the fourth for women between 45 and 64 years-old. They emphasized the necessity for a conscious prescription of BZD from the health professionals.

Linden et al. (1994) used data from the "Psychological Problems in General Health Care" (PPGHC), a multicenter study (Sartorius et al. 1993) coordinated by the World Health Organization (WHO) in 15 centers from 14 countries, including one in the city of Rio de Janeiro. The study observed that the general practitioners prescribe a large sample of psychotropic drugs for the treatment of psychiatric disorders. The anxiolytic, hypnotics and antidepressant drugs were mostly prescribed. Each of these categories of medications represented 20% of the total prescriptions. Antipsychotics, analgesics and phytotherapeutic drugs were prescribed in 5 to 10% of the prescriptions. In the same study, the amount of prescriptions for each psychiatric disorder based in the Tenth edition of the International Diagnostic Classification (ICD-10) varied from 19.3% for the recurrent depression to 55% for the agoraphobia. Only 7.7% of the patients with anxiety disorders received a prescription of an antidepressant while 34.1% received a BZD. Among the patients with depressive disorders, 31.9% and 25.5% received a prescription of an antidepressant and of a BZD, respectively. These data show a high prescription of BZD for the patients with depression. It was also observed that many prescribed drugs had no evidence of the efficacy, like phytotherapeutic drugs and analgesics (35.6% of all prescriptions). The acknowledgment of the mental disorder diagnosis is very important but not enough to lead to the proper treatment.

Kisely et al. (2000) have also made another analysis of some other factors associated with the prescription of psychotropic drugs in these

multicenter data (Sartorius et al. 1993). A sample of 1,781 patients presented evident psychological and psychiatric symptoms. The main factors associated to BZD prescription in that sample were: old age, female, unemployment and loss of a partner by divorce or death. The clinical features mainly associated were only depression and psychotic disorders.

Another data scrapped from this study (Kisely et al. 2000) is that more anxiolytics were prescribed to anxiety disorder patients, female, and subjects with less year-of-study and unemployed. The general physicians, who recognized their psychiatric knowledge more important to their daily practice and prescribed less anxiolytics. This may demonstrate the importance of the psychiatric studies during medical school. Main contribution of this study was to show the importance of social-demographic and clinical aspects of each prescription.

Valle et al. (1998) also studied the association between BZD and depression in 91 patients who used BZD. They observed that 40.7% of these patients had major depression, especially women with a high use BZD.

Our trial was conducted in The Outpatient General Medicine Unit of the Severino Sombra University Hospital-Vassouras (Brazil, RJ). We describe the prevalence of BZD use between August 2004 and December 2006, patient's anxiety disorders and depression prevalence, and compare their features with the patients who did not use BZD.

MATERIAL AND METHODS

In order to review the literature we searched the PubMed/Medline with the keywords: benzodiazepines; psychotropic drugs; anxiolytic drugs; psychotropic medication; general health; general practice; primary care; anxiety; depression; and mental disorder. We crossed the key-words in the database and we also searched the Related Articles section. The references of the articles were also used as source data for our review.

We randomly selected 103 outpatients from The Outpatient General Medicine Unit of the Severino Sombra University Hospital. The patients

included were of both the genders with ages between 18 and 70 years, who were there for the treatment of any complain or disorder. We only included patients that could answer the interview by themselves (patients with delirium or who could not speak were not included). After they agreed to participate in our protocol they signed a written informed consent. The protocol was approved by our local ethics committee.

The patients were then interviewed in a structured diagnostic clinical questionnaire: Mini International Neuropsychiatric Interview (Sheehan et al. 1996) - MINI - which has a pattern for evaluation of each diagnostic criterion the Axis I diagnosis of DSM-IV(1994). The socio-demographic features, present and past pattern of BZD use, the history of previous psychiatric treatment were obtained by a questionnaire developed by the authors. High educational level was considered when the patient had at least elementary school.

STATISTICAL ANALYSIS

We used de SPSS Program version 13.0. The χ^2 test with Yates correction was used for categorical data analysis. The Student-t test was used for the analysis of continuous data. The level of significance was set at 5%.

RESULTS

The patients (n=103) were 52 (50.5%) men and 51 (49.5%) women (Table 1). The mean age (\pm SD) was 44.4 (\pm 16.6) year-old. 58.3% (n=60) of the patients denied present or past use of BZD; 26.2% (n=27) were currently using BZD; and 15.5% (n=16) stated previous use of BZD. We detected with the MINI that 39.8% (n=41) had a psychiatric diagnosis. The most frequent ones were depression (n=22, 21.4%), generalized anxiety disorder (GAD) (n= 26, 25.0%), agoraphobia (7.8%, n=8) and alcohol dependence disorder (n=3, 2.9%) - **Table 1**. In the group of patients with a psychiatric diagnoses (n=41), 46.3% had at least one psychiatric comorbidity mainly depression and GAD (68.4%, n=13).

The total sample (n=103) was divided in two groups: one group of the patients who had never used BZD (n= 60, 58.3%) and the other group of patients with current or previous use of BZD (n=43, 41.7%). The first group who had never used BZD was significantly younger (40.1 ± 16.2 year old vs. 50.3 ± 15.4 year old, $p=0.002$).

No significant differences in gender, educational level, and occupation between the groups were found. The group with current or previous use of BZD had significantly more anxiety disorder diagnoses ($p=0.028$), depression ($p=0.019$) and agoraphobia ($p=0.047$).

Table 1. Demographic and clinical features in the patients who had never use benzodiazepines (BZD) (n=60) and in the patients with previous or current use of BZD (n=43).

	Never used BZD (n=60)	Previous or current use of BZD (n=43)	P
Age (mean \pm SD)	40.1 (\pm 16.2)	50.3 (\pm 15.4)	0,002 ¹
Gender	n (%)	n (%)	
Male	34 (56.7)	18 (41.9)	ns ²
Female	26 (43.3)	25 (58.1)	
Educational Level			
Low	29 (48.3)	28 (65.1)	ns ²
High	31 (51.7)	15 (34.9)	
Marriage state			
Single	23 (38.3)	9 (20.9)	ns ²
Married	30 (50.0)	25 (58.1)	
Divorced	4 (6.7)	2 (4.7)	
Widow(er)	3 (5.0)	7 (16.3)	
Occupation			
Active with salary	35 (59.3)	17 (39.5)	ns ²
Active without salary	6 (10.2)	11 (25.6)	
Inactive	18 (30.5)	15 (34.9)	
Current Mental Disorder			
Anxiety disorder	17 (28.3)	24 (55.8)	0,005 ²
Depression	13 (21.7)	18 (41.9)	0,028 ²
Dysthymia	8 (13.3)	14 (32.6)	0,019 ²
Dysthymia	2 (3.3)	0 (0.0%)	ns ²
Maniac episode/hypomania	2 (3.3)	1 (2.3)	ns ²
Generalized Anxiety Disorder	2 (3.3)	1 (2.3)	ns ²
Panic disorder	13 (21.7)	13 (30.2)	ns ²
Agoraphobia	1 (1.7)	2 (4.7)	ns ²
Post Traumatic Stress Disorder	2 (3.3)	6 (14.0)	0,047 ²
Obsessive Compulsive Disorder	0 (0.0)	1 (2.3)	ns ²
Alcohol dependence	0 (0.0)	1 (2.3)	ns ²
Cocaine dependence	1 (1.7)	2 (4.7)	ns ²
Suicide risk	0 (0.0)	1 (2.3)	ns ²
Suicide risk	4 (6.7)	4 (9.3)	ns ²

¹ t test; ² Chi square
ns – not significant (>0.05).

In the first BZD prescription, 69.8% (n=30) patients said that it was prescribed by their general physician and 21% (n=9) by a psychiatrist. Among the patients who were currently using BZD, 37.0% reported they were concomitantly being treated in a psychiatric outpatient clinic. The main BZDs used or being used by the patients were diazepam and bromazepam.

Among the patients who used or were currently using BZD, 42.0% (n=18) said they used BZD from some days to six months; 23.0% (n=10) said they used it for five or more years. The daily use was found in 55.8% (n=24) patients and 44.1% (n=19) referred occasional use. Among the reasons for the BZD use were insomnia (67.4%, n=29), "nervous breakdown" (72.0%, n=31), depression (39.5%, n=17) and headache (14.0%, n=6). The main adverse events associated with the use of BZD were somnolence (74.4%, n=32) and dizziness (23.2%, n=10).

DISCUSSION

Our study observed a high frequency of patients with current and previous use of BZD in a Primary Outpatient Care Unit. In our sample 41.7% referred current or previous use of BZDs and they were significantly older than the group who had never used BZD. One possible explanation for this finding is that the older group could have more somatic complains including insomnia and headache or asked directly for BZD from physicians.

One interesting observation was that almost 70% of the patients had their first BZD prescription from the general physician while complaining of insomnia, "nervous breakdown", depression and headache. The period of time for BZD use was more than five years in 22% of patients who used or were using BZD and 55.8% referred daily use. It is possible that some of these patients already had BZD dependence.

A high psychiatric morbidity in our sample was also found. The prevalence of depression (21.4%) and anxiety disorders (30.1%) in BZD

dependant patients was higher than the general population (Weissman et al. 1997). A previous study in two asthma university outpatient clinics observed a high prevalence of major depression (24.0%), GAD (20.9%) and the panic/agoraphobic spectrum (17.7%) (Valença et al. 2006). Our data are in concordance with previous studies (Gabarron et al. 2002; Nascimento et al. 2002) and demonstrate the importance of a psychiatric examination for patients who look for the treatment in a primary outpatient care unit. One point that shows us that our group with previous or current used of BZD had significantly more mental disorders than the group who had never used BZD.

Kroenke et al. (2007) also observed a high prevalence of anxiety disorders in patients from a primary care unit. In a large sample of 965 patients, 19.5% had at least one anxiety disorder: 8.6% post traumatic stress disorder; 7.6% GAD; 6.8% panic disorder; and 6.2% social anxiety disorder. Each disorder was associated to a severe deficit in functioning and limitations. This deficit increase when associated to anxiety disorder comorbidities. In our trial we found that 30% of our samples had anxiety disorders, demonstrating the strong association between somatic illness and these disorders.

The patients who are assisted in a primary care unit usually have somatic complains. Katon et al. (2007) reviewed 31 trials with a total of 16,900 patients with several chronic illnesses such as diabetes, coronary heart disease, congestive heart failure, asthma and osteoarthritis. They found that these patients with comorbid anxiety and depressive disorders have more somatic complains when compared to those with only chronic somatic illness. It is possible that this comorbid feature influences the prescription of BZD in those patients as we found in our study.

It is also substantially documented that the majority of patients with mental disorders or psychological problems are more assisted by their general physician than by a psychiatrist (Goldberg et al. 1976). Some regional research trials have shown that psychotropic drugs have a special role in the treatment of mental disorders and that the medical staff from a primary care unit is responsible for the

prescription of the majority of these drugs including the BZD (Joukamaa et al. 1995).

Zitman and Couvée (2001) described that a high proportion of chronic benzodiazepine users suffer from depression. For these patients, BZDs are not the adequate treatment. The therapeutic value of the chronic use of these drugs is questionable and the BZDs are not recognized as effective antidepressants. The chronic users of BZD should be examined in order to diagnosis associated mental disorders and to consider a proper treatment. We should have in mind that the depression disorder is usually associated to some anxiety symptoms. Ormel e col. (1991) showed that in 1,994 patients, only 47% with anxiety disorders or depression had their mental diagnosis identified by their general practitioners. The patients who had mental diagnosis were identified by their clinician and had a shorter episode of their anxiety disorder and a higher probability of receiving adequate psychiatric treatment.

Other clinical and epidemiological trials that could help the general physician in the early diagnosis and treatment of anxiety disorders and depression in patients with somatic illness may be very useful for the public health care. It is worthwhile to recognize the fundamental aspects of diagnosis and treatment of anxiety disorders and depression by the medical staff in a primary care unit. The identification and the treatment of these disorders in patients with somatic illness can significantly contribute to improve their general health and quality of life.

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