

A COMPREHENSIVE STUDY ON BENZODIAZEPINE USE IN THE ROMANIAN GENERAL POPULATION

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Abstract

The aim of this study was to assess the main characteristics of the current use of benzodiazepines and the levels of benzodiazepines (BDZs) dependency in a group of Romanian drug users who take BDZs.

A questionnaire was compiled which sought information on sociodemographic details, the type of the BDZ used, the frequency and the duration of use. The second part of the questionnaire was represented by The Benzodiazepine Dependence Questionnaire (BDEPQ) - a 30-item self-report questionnaire for measuring dependence on BDZ tranquilizers, sedatives and hypnotics. The respondents received the questionnaire while they came with a prescription for one or more BDZs in one of eight community pharmacies in Cluj participating of the study.

The results were subjected to appropriate statistical tests of significance including multivariate statistics (factor analysis, principal component analysis) and Rasch analysis. The results showed that, despite precautions, warnings and attempts to limit use, there remains a high proportion of long-term BDZ users, especially in the elderly population.

Keywords: benzodiazepines, dependency, questionnaire, statistics.

UN STUDIU COMPREHENSIV ASUPRA UTILIZĂRII BENZODIAZEPINELOR ÎN POPULAȚIA GENERALĂ DIN ROMÂNIA

Rezumat

Scopul acestei lucrări a fost de a stabili principalele caracteristici ale consumului și ale gradului de dependență, pe un eșantion de pacienți aflați sub tratament cu benzodiazepine.

Evaluarea utilizării benzodiazepinelor s-a efectuat pe baza unui chestionar complex, care cuprinde detalii socio-demografice, tipul benzodiazepinelor utilizate, durata și frecvența administrării. Cea de-a doua parte a chestionarului este reprezentată de The Benzodiazepine Dependence Questionnaire (BDEPQ) – un chestionar de referință, cu 30 de întrebări, menit să evalueze dependența de benzodiazepinele utilizate ca tranchilizante, sedative și hipnotice. Chestionarul a fost înmănat respondenților după eliberarea benzodiazepinelor prescrise, într-una din cele opt farmacii din Cluj-Napoca participante la studiu.

Rezultatele obținute evidențiază faptul că, în ciuda precauțiilor și a eforturilor de a limita utilizarea benzodiazepinelor, rămâne un procent însemnat de consumatori, mai ales printre persoanele vârstnice.

Cuvinte cheie: benzodiazepine, dependență, chestionar.

INTRODUCTION

Benzodiazepines (BDZs) were developed in the early 60's as a treatment for anxiety. Nowadays, because their efficacy and tolerability are generally good, benzodiazepines (BDZs) are among the most widely used drugs in the general population as anxiolytics, sedative-hypnotics, anticonvulsivants and myorelaxants [1].

When benzodiazepines were initially introduced in clinical practice, they were thought to be free of addictive properties. However, since the early 1970s, it has been clear that these compounds could produce psychological dependence and withdrawal symptoms. Dependence can develop to therapeutic doses of benzodiazepines, after 4 to 6 weeks of regular usage, but it may develop more rapidly to very high doses administered for a shorter period of time or in the case of individuals who have been previously dependent on other sedatives or alcohol [2].

In addition to the dependence, there are many adverse drug reactions related to BDZ use such as cognitive impairment, reduced functional autonomy, falls and hip fractures, psychomotor slowing, delirium, hospitalizations, car accidents and higher suicide rates [3].

The first objective of this study was to assess the particularities of the benzodiazepines consumption in a sample of Romanian drug users taking BDZs; the second objective was to set a correlation between the use of the BDZs, the sociodemographic factors and the level of dependency on BDZs quantified through The Benzodiazepine Dependence Questionnaire (BDEPQ). To our knowledge, this is the first reported study on benzodiazepine use and dependency associated with this use developed through community pharmacies.

MATERIALS AND METHODS

Study design and population

The study was conducted between June and December 2010. The target population was composed of the patients who came with a prescription for one or more BDZs in one of eight community pharmacies in Cluj included in the study. A total of 150 questionnaires were distributed through participating pharmacies and 68 questionnaires completely filled were returned. The participation in the study was anonymous and voluntarily. The respondents were asked to respond to the questions thinking about their experience on BDZs from the last month.

Data collection

The questionnaire was developed based on similar studies reported in the literature [4-7,8,9,10,11-19,20,21,3].

The first part of the questionnaire summarized the sociodemographic profile, the type of the BDZ used, the frequency and the duration associated with this use. The second part of the questionnaire was represented by The Benzodiazepine Dependence Questionnaire (BDEPQ) developed by Baillie and Mattick (1996) [6], with the

aim to reflect the severity of BDZ dependence and the psychological, physiological and social aspects of BDZ dependence. The high reliability and validity of the BDEPQ support its use as a research instrument.

The BDEPQ asks respondents to think of their experiences with BDZ use in the past month and rate their responses to items based on a four-point Likert scale with a variety of different response options. Most items are scored by assigning 0 (never), 1 (sometimes), 2 (often), 3 (always) except for items 2, 5, 6, 9, 12, 16, 17 and 23, which are scored in reverse. The question 14a is not scored. The main areas of the dependence syndrome covered by the BDEPQ are: general dependence subscale, pleasant effects subscale and perceived need subscale. A total score and three subscale scores can be calculated. However, given the preliminary nature of the scale, test scores should be interpreted with precaution in a general manner [6,22,23,24,1,25,26,27].

BDZ use

Patients who declared the use of one or more BDZ in the last month were considered current users of BDZs. The patients were asked to give information about the BDZ used, the daily dose and the frequency of use.

Statistical data

As in the majority of questionnaires used today in survey research, BDEPQ is Likert-type psychometric scale based. When responding to an item, patients specify their level of agreement or disagreement on an agree-disagree scale.

All data analyses were conducted using SPSS Statistics 19 with the exception of the Rasch analyses, which were conducted using jMetrik 2.1.0. Initial factor analyses were used to explore variability among observed variables in order to identify the main factors. These were followed by Rasch analyses to test the reliability.

Factor analysis

Factor analysis is used to describe variability among observed variables in order to potentially describe a lower number of unobserved variables called factors.

The three main components influencing the benzodiazepine dependence, general dependence, perceived need and pleasant effect, described as sub-scales in the BDEPQ documentation and several other papers [6,25,20] are considered to be factors. For our purpose, factor analysis is used in order to check if these are truly the most important factors which influence our patients' dependence on benzodiazepines and to what extent.

In accordance with the 3-factor structure of the BDEPQ, we developed and carried out a statistical factor analysis of forced-factor principal component analysis type with varimax rotation. Items were allocated to factors taking into account the higher loadings (Table I) [28].

The factor analysis is mixed involving first an exploratory factor analysis (EFA) and after a confirmatory factor analysis (CFA), as we first identified the factors through EFA and then we used the forced factor-principal

component analysis to confirm that the three main factors described in the literature were explaining most of the variance in our data through CFA.

For factoring, we used a principal component analysis (PCA), the main method used in similar studies. It is mostly used in EFA when a researcher wants to reduce a large number of items to a smaller number of latent dimensions. This method seeks a linear combination of variables, as the different answers from our patients, such as the maximum variance is extracted from the variables. This variance is then removed and a second linear combination which explains the maximum proportion of the remaining variance is extracted. Then, the variance is removed and a third linear combination is extracted and so on.

As the total variance in our patient's answers was statistically significant, we used this factor analysis-PCA in order to identify the main factors responsible for the variance. Those factors can also be interpreted to explain the general dependence and causes of dependence in our patients.

In order to be able to differentiate the original variables, which in our case are represented by the items in the BDEPQ questionnaire, by extracted factors (general dependence, perceived need and pleasant effect) we used the varimax rotation. This is an orthogonal rotation of the factor axes to maximize the variance of the squared loadings of a factor on the entire variable.

To identify properly the number of factors influencing the dependence of our patients we used the screen plot resulted from EFA. The curve showed a change in decrease starting with factor three, thus suggesting this number as the number of the main factors to explain the variance and dependence in our patients.

Rasch analysis

The Rasch Analysis is one of the analyses used in Item Response Theory (ITA) to estimate the probability of a correct answer to a given item (in this case question in BDEPQ) as a function of item difficulty and personal ability. The purpose of applying the Rasch model is to obtain measurements from categorical response data. The advantage of using the Rasch analysis is that the sum score reflects all information contained in the item scores [20].

Reliability of the total score and subscales of the BDEPQ was obtained by Cronbach's coefficient alpha using "Item Analysis" function in jMetrik software. This is a coefficient of reliability and it is used to measure the internal consistency of a psychometric test given at a sample of examinees. Cronbach's coefficient alpha will increase as the intercorrelations between test items increase. Because these correlations are at maximum when all items measure the same construct, Cronbach's coefficient alpha indicates the degree to which a set of items measures a single unidimensional latent construct, in our case the dependency.

RESULTS AND DISCUSSION

Construction validity of the BDEPQ

Most of the items loaded on the factors originally proposed: perceived need (Factor I), pleasant effects (Factor III) and general dependence (Factor II). The items 21a and 21b loaded in the perceived need subscale. The forced three-factor analysis explained 49.13% of the total variance (Table I).

Reliability of the BDEPQ

The BDEPQ proved to have good reliability: Cronbach's coefficient alpha for the total score was high (0.91). The perceived need subscale had a coefficient alpha of 0.89, followed by 0.82 of the general dependence subscale and finally, a coefficient alpha of 0.80 for the pleasant effects subscale.

The results of the Rasch analysis are presented in Table II:

Table II. Rasch model results.

SCALE QUALITY STATISTICS		
Statistical parameter	Items	Persons
Observed Variance	0.5615	1.0849
Observed Std. Dev.	0.7493	1.0416
Mean Square Error	0.0289	0.0858
Root MSE	0.1699	0.2928
Adjusted Variance	0.5326	0.9992
Adjusted Std. Dev.	0.7298	0.9996
Separation Index	4.296	3.4134
Number of Strata	6.0613	4.8845
Reliability	0.9486	0.921

The results obtained support the tridimensional model underlying the approach of BDZ use assessed by the BDEPQ. The perceived need component (Factor I) has the most prominent influence in the BDZ dependence (20.37%) and has the highest reliability from the subscales of the BDEPQ (0.89). The perceive need explain the patients' belief that they cannot function without BDZs. Benzodiazepine users probably can develop a behavioral addiction to the practice of taking the pill in addition to a psychological and physiological addiction to the active compound [8]. In this case, it is important to distinguish the patients that really perceive the need to take benzodiazepine and those who developed a behavioral addiction due to the chronic administration of the drugs.

The general dependence (Factor II) was second in order of importance (16.17%) and shows a good reliability (0.82). The general dependence component reflects many aspects of the WHO dependence syndrome like the tolerance and the avoidance of withdrawal syndrome. Current definitions of dependence consider it as a psychological and behavioral syndrome specifically characterized by a loss of control over drug use, compulsive drug use, and continued use despite harm.

The pleasant effect subscale (Factor III) is the third in the order of importance (12.59%) and score the

Table I. Factor loadings of BDEPQ items in the three-factor model – Varimax.

Question	Component		
	I	II	III
1. In the last month, have you taken another sedative or tranquillizer as soon as the effects of the previous one began to wear off?	-0.003	0.657	-0.088
2. Have you taken sedatives, tranquillizers or sleeping pills in the last month because you like the way they make you feel?	0.235	0.083	0.660
3. Have you felt you cannot face anything out of the ordinary without a sedative or tranquillizer?	0.761	0.080	0.210
4. Do you feel that you cannot get through the day without the help of your sedative or tranquillizer?	0.860	0.154	0.135
5. Do you need to carry your sedatives or tranquillizer with you?	0.590	0.200	0.213
6. Have you tried to reduce the number of sedatives, tranquillizers or sleeping pills you take because they interfered with your life?	0.347	-0.246	0.141
7. Have you found that you needed to take more tranquillizers, sedatives or sleeping pills to get the same effect in the last month compared to when you first took them?	-0.059	0.696	0.115
8. Do you need to take sedatives, tranquillizers or sleeping pills to deal with the problems in your life?	0.815	0.056	0.118
9. Do you feel terrible if you do not take a sedative, tranquillizer or sleeping pill?	0.804	0.108	0.248
10a. In the last month, have you been worried that your doctor might not continue to prescribe the sedatives, tranquillizers or sleeping pills you are taking?	0.378	0.638	0.255
10b. How strong has this worry been?	0.295	0.683	0.284
11. Could you stop taking sedatives, tranquillizers or sleeping pills tomorrow without any difficulties?	0.613	0.263	0.160
12. Do you count down the time until you can take your next sedative, tranquillizer or sleeping pill?	0.337	0.116	0.576
13a. Have you experienced relief when you have taken sedatives, tranquillizers or sleeping pills in the last month?	0.231	0.002	0.679
13b. How strong is that relief?	0.102	0.263	0.674
14b. Have you taken another sedative, tranquillizer or sleeping pill to reduce these unpleasant after-effects?	0.050	0.721	0.082
15. In the last month, have you taken sedatives, tranquillizers or sleeping pills against your doctor's advice or more frequently than recommended?	0.184	0.569	0.118
16. Are you concerned about the number of sedatives, tranquillizers or sleeping pills you have taken in the last month?	0.117	0.354	0.042
17. Have you taken more sedatives, tranquillizers or sleeping pills in 1 day or night than you planned to?	0.455	0.310	0.040
18a. Have you found the effects of sedatives, tranquillizers or sleeping pills pleasant?	0.089	-0.073	0.793
18b. How strong is the pleasant feeling?	0.077	0.271	0.770
19. Have you taken sedatives, tranquillizers or sleeping pills for a longer period than you intended to when you started?	0.583	0.284	-0.072
20a. Have you felt tense or anxious as your prescription for sedatives, tranquillizers or sleeping pills began to run out?	0.513	0.502	0.284
20b. How strong have these feelings been?	0.522	0.579	0.259
21a. Have you felt an urge or a desire to take sedatives, tranquillizers or sleeping pills in the last month?	0.730	0.101	0.367
21b. How strong is that urge? (...to take sedatives, tranquillizers or sleeping pills)	0.442	0.359	0.320
22. Have you taken sedatives, tranquillizers or sleeping pills in the last month when you did not really need them?	0.094	0.279	0.221
23. I feel powerless to prevent myself taking a sedative or tranquillizer when I am anxious, uptight or unhappy.	0.207	0.482	0.033
24. I would not be able to handle my problems unless I take a sedative or tranquillizer.	0.479	0.395	0.120
25. I get so upset over small arguments that I need to take a sedative or tranquillizer.	0.127	0.586	0.035
Eigenvalue	6.11	4.85	3.77
Variance (%)	20.37	16.17	12.59

administration of BDZ in order to feel a pleasurable effect.

This study was limited by the relatively small sample size and the inclusion of several psychiatric diagnoses. To be able to interpret results in a more restrictive manner and to set the level of the dependence of the patients, it is necessary to compare the results with standards obtained after psychiatric diagnosis made with the Structured Clinical Interview for DSM-IV Axis-I Disorders (SCID-I) [25]. Due to the fact that our patients were voluntary and anonymous participants in the study we couldn't carry out a psychiatric evaluation in order to compare our results with SCID-I diagnoses of BZD dependence. Our study can be developed further by including experts in the field of psychiatry and following the guidelines obtained as a result of the current study.

Characteristics of BDZ consumption

The sociodemographic characteristics of the study population are shown in Table III. The mean age of the BDZ consumers was 62.4±16.3years (25-88 years). Consumption was higher among women (75 %) than men (25%). BDZ use increased with age and the prevalence of BDZ use was higher in married than in single persons. A total of 82% had children and the majority of BDZ users (78%) were not living alone. Regarding the level of education, the majority of BDZ consumers (85%) had secondary or university studies.

Table III. Baseline demographic, social and professional characteristics of the total sample (n=68) included in study.

	Study sample(n= 68) (% of sample)	
Age (mean \pm SD)	62.4 \pm 16.3	
25–30	1	(1.5)
31–40	6	(8.8)
41–50	4	(5.9)
51–60	18	(26.5)
61–70	22	(32.4)
71–88	17	(25)
Gender		
Male (%)	17	(25)
Female (%)	51	(75)
Marital/social status (%)		
Single/never married	5	(7.4)
Married	43	(63.2)
Divorced	5	(7.4)
Widowed	15	(22)
Children		
Yes (%)	56	(82.4)
No (%)	12	(17.6)
Living arrangement (%)		
Alone	15	(22)
Not alone	53	(78)
Level of education (%)		
Primary (General school)	10	(14.7)
Secondary (High school)	33	(48.5)
Advanced (University& Postgraduated studies)	25	(36.8)

Table IV. Clinical characteristics of the total sample (n= 68) included in study.

Variable	Category	Study sample (n= 68)
Benzodiazepine used	Alprazolam	22
	Bromazepam	11
	Clonazepam	5
	Clorazepate	4
	Diazepam	8
	Lorazepam	8
	Medazepam	1
	Midazolam	3
	Nitrazepam	5
	Zolpidem	10
	Zopiclone	8
More than one benzodiazepine	No	56
	Yes	12
Antidepressant use	No	55
	Yes	13
Chronic medical conditions	No	23
	Yes	45
The reason of use	Anxiety disorders (including panic disorders)	24
	Depressive disorders	18
	Personality disorders	1
	Sleeping disorders	41
	Other	4
The frequency of use	Every day (6–7 days/week)	32
	4–5 days/week	12
	1–3 days/week	14
	Less than once/week	10
The duration of use	Less than one month	6
	More than one month but less than 3 months	7
	More than 3 months but less than 6 months	5
	More than 6 months	34
	Not known	16

The most common benzodiazepines used by the patients in our study: alprazolam, bromazepam and zolpidem accounted for 50.6% of the total use. From the total number of patients, a percent of 17.6% were using more than one benzodiazepine at the same time, while 19.1% of the sample was using antidepressants concomitantly. One patient was using three benzodiazepines in the same time associated with one antidepressant. Almost two thirds of the patients were affected by a chronic medical condition such as hypertension, diabetes and ischemic heart disease, mainly due to age (the mean age of the patients in the study was 62.4 years).

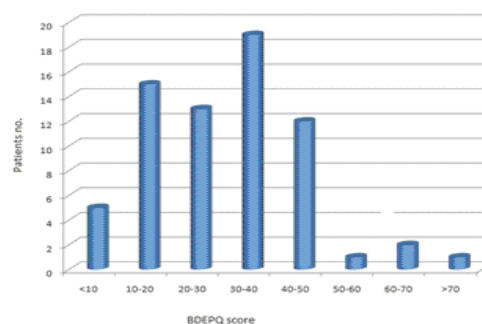
The majority of patients declared that they used the benzodiazepines for the management of insomnia (60.3%) and anxiety disorders (35.3%), every day of the week (47.1%) and for more than 6 months ago (50%).

Considering the epidemiological characteristics as potential risk factors and by frequency and statistic confirmation we could create a standard profile for a BDZ consumer:

- gender: female
- age: 62 years
- marital status: married, with children
- level of education: high school
- benzodiazepine used: alprazolam
- the reason of use: insomnia
- the frequency of use: every day

The BDEPQ score

The BDEPQ score varies between 1 and 74 while the medium score obtained is 29.75 (\pm 15.36). BZD dependency is a multidimensional construct but there are many instances where interpretation is made easier by means of a cut-off score. Taking into account the average score and cut off values determined in similar studies [25], we consider that for the purpose of this study a cut off value of 23 discriminate between dependent and non dependent patients. The three subscale scores were also calculated. The higher frequencies were recorded under the total score of 40 (76.5% of cases), which indicates a low to medium dependency. Higher scores indicate individuals with a higher risk of presenting withdrawal symptoms in a future and a CIDI (The World Health Organization (WHO) Composite International Diagnostic Interview) diagnosis of BDZ dependence. The distribution of cases according with the total BDEPQ score is presented in Figure 1.

**Fig 1.** The distributions of patients according to BDEPQ score.

The goal of the study was to assess the main characteristics of the current use of benzodiazepines and the levels of benzodiazepines (BDZs) dependency. The present study is useful for the detection of patients vulnerable to BZD dependence and for the early recognition of the dependence.

CONCLUSIONS

Our study suggest that validated structured questionnaires like BDEPQ, may be a rapid and simple way to obtain data on current medication use directly from patients and to assess an evaluation of the BDZ consumption.

The results showed that, despite precautions, warnings and attempts to limit use, there remains a high proportion of long-term BDZ users. As is the case elsewhere, BZD use by the patients in our study is concentrated in the elderly and on long-term use, where the risks are highest and the possible benefits lowest.

The main factor of the BDZ use is the belief of the patients that they cannot function without BDZs. Alprazolam is the most frequently used BDZ and the declared scope of use is the management of insomnia.

Recognition of patient risk factors, careful patient screening and careful monitoring of prescriptions are valuable strategies for the activity of the pharmacists in order to minimize the benzodiazepine abuse and dependence.

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