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Use of Benzodiazepines in Patients with Bipolar Disorder

Abstract

Introduction: Benzodiazepines (BZDs) are widely used in patients with bipolar disorder. The aim of this study was to determine chronic use of Benzodiazepines (BZDs) in patients with a first bipolar episode and the association between its use and cognition.

Methods: A prospective longitudinal study was conducted in a cohort of 63 patients under 40 years old with a first manic or mixed episode. The percentage of patients taking Benzodiazepines (BZDs) in the baseline sample was evaluated at 6 months and for the next 3 years. Cognitive functioning was compared between patients with chronic Benzodiazepine (BDZ) use and those who did not use them. A linear regression model adjusted for potential confounding variables such as age and education level were used.

Results: Just over half the sample (55.6%; n=35) took Benzodiazepine (BZD) at the start of the study. At 6 months, this percentage decreased to 34.9% (n=22) and to 14.3% (n=9) at 3 years of follow-up. Patients who took Benzodiazepine (BZD) chronically had worse outcomes in overall attention. These differences remained significant when controlled for the variables age and education level (B= -0.462, p=0.046, 95% CI: -0.914, -0.009).

Conclusion: Chronic administration of Benzodiazepine (BZD) occurs in a small percentage of bipolar patients at disease onset and is associated with decreased attention. These side effects should be followed up.

Keywords: Bipolar disorder; Benzodiazepines; Cognition; Prolonged use; Overall attention

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Introduction

Benzodiazepines (BZDs) are widely used drugs for the treatment of anxiety, sleep disorders, adjuvant therapy in patients with depression/mania and as muscle relaxants [1]. These drugs are considered effective and safe in short term use; however, their long-term use is associated with adverse health outcomes [2-4]. Clinical guidelines recommend that Benzodiazepines (BZDs) treatment should be kept as short and at the lowest dosage possible [1]. Benzodiazepines (BDZs) are commonly used in patients with bipolar disorder and it should be noted that cognitive disorders are a possible side effect of Benzodiazepines (BZDs) and could worsen the prognosis for such patients [5,6]. Although there are other factors associated with these patient's cognitive disorders, such as chronicity or the frequency of relapses, it is with the pharmacological treatment received where we can intervene most. Memory, attention and psychomotor disfunctions are also related with the use of Benzodiazepines (BDZs) [2,3].

Our aim was to establish the incidence of acute and chronic use of Benzodiazepines (BZDs) in patients who suffered a first bipolar episode. In addition, we studied the possible association between long-term Benzodiazepines (BZDs) use and changes in cognitive factors of these patients.

Methods

A three-year prospective longitudinal study was performed in a cohort of 63 patients under the age of 40 that had suffered a first maniac or mixed episode. The patients who met DSM-V

Diagnostic Criteria of A First Maniac or mixed episode, who were diagnosed and treated consecutively either in the hospitalization unit or the partial hospitalization unit, also had to meet the following criteria in order to be part of the cohort: Aged between 18–40 speak Spanish correctly and provide formal consent to participate in the present study [7]. The exclusion criteria used were presence of organic central nervous system diseases, cranial-encephalic trauma with loss of consciousness, mental retardation, widespread development disorders, pregnancy and breastfeeding. We compared the differences in cognitive functioning in patients who received acute and chronic treatment with Benzodiazepines (BDZs) at three specific periods of time: Baseline, 6 months and 3 years of follow-up. Duration of 6 months or longer was established to define chronic use of Benzodiazepines (BZDs).

The Declaration of Helsinki rules were used by our ethics committee in order to approve the design and authorization of this study.

Statistical analysis

Sociodemographic variables were described as averages (± standard deviation) and percentages. To analyze the differences between the two groups, Student t tests were used for independent samples in quantitative variables and Chi-square tests for qualitative variables. The comparison of the use of Benzodiazepines (BZDs) in the three follow-up visits was made with Chi-square tests. The study of cognitive functioning was carried out by creating eight cognitive domains. In order to develop the study correctly, the mean z scores of the neuropsychological variables for each domain used were calculated. Finally, the domain "Overall Cognition" was calculated by performing an average of the scores of the previous seven domains. The influence of chronic Benzodiazepines (BZDs) treatment on the different cognitive domains was analyzed by linear regressions. Initially, potentially confusing variables were included in the different domains, however only the ones which were significant after the different steps of the process were included in the final model. The results are shown as B coefficient, p-value and 95% confidence interval. All analysis were performed with the SPSS v.23 Statistical Program, considering the level of significance of $p < 0.05$.

Results

38% of the sample were women (n=24) and the average age was 28.21 ± 7.98. In the non-BZD treated group 40% of patients had primary studies (n=8), while in the Benzodiazepines (BZDs) treated group this percentage was reduced to 9.8% (n=4). There were no differences between the two groups in terms of toxic substances consumption and adherence (Table S1).

55.6% of the sample (n=35) was under Benzodiazepine (BZD) treatment at the beginning of the study. After six months of follow up, this percentage decreased to 34.9% (n=22) and to 14.3% (n=9) after 3 years. During follow-up, 66.7% (n=42) of patients took Benzodiazepine (BZD) for 6 months or more (Figure S1).

When comparing Benzodiazepine (BZD) intake between each patient visit, 85% (n=24) of the patients who did not take Benzodiazepine (BZD) at baseline did not do so after 6 months of follow up. However, in the group that did take BZD at baseline, 48.3% (n=17) left the Benzodiazepine (BZD) treatment after 6 months (X2=9.443, p=0.002). Regarding the visits performed at 6 months and 3 years, 90% (n=37) of those who did not take Benzodiazepine (BZD) at 6 months, did not do so at the end of follow-up, while in the group that did take Benzodiazepine (BZD) at 6 months, 77% (n=17) did not have this treatment at 3 years, there were no significant differences between the two groups (X2=1.967, p=0.161).

Patients with chronic Benzodiazepine (BZD) treatment recorded worse results in all cognitive domains **(Table 1)**, becoming this significant difference in overall attention (t=2.481, p=0.020) **(Figure 1)**. In addition, after the inclusion of age and level of studies as confusion variables in the linear regression models, the result remained significant, showing again that patients with continued Benzodiazepine (BZD) treatment (2 or more visits in a row) were associated with a lower score in overall attention (B= -0.462, p=0.046, 95% CI: -0.914, -0.009). Non-significant relationships were observed in the rest of domains, although there was a tendency to show significant results regarding working memory and in overall cognition. These two domains were associated with reduced cognitive capacity in patients under Benzodiazepine (BZD) treatment.

Variable average ± SD	Total (n = 63)	No BZD (n = 21)	Yes BZD (n = 42)	Statistics
Overall attention	0.29 ± 0.52	0.57 ± 0.28	0.18 ± 0.56	t=2.481; p = 0.020
Processing speed	0.03 ± 0.74	0.30 ± 0.55	-0.07 ± 0.79	t=1.241; p = 0.225
Working Memory	-0.03 ± 0.75	0.33 ± 0.59	-0.16 ± 0.76	t=1.646; p = 0.111
Executive functions	-0.71 ± 0.42	-0.65 ± 0.56	-0.75 ± 0.34	t=0.529; p = 0.603
Short term memory	-0.19 ± 0.79	0.02 ± 0.75	-0.27 ± 0.81	t=0.875; p = 0.389
Long term memory	-0.62 ± 0.90	-0.23 ± 0.72	-0.76 ± 0.93	t=1.450; p = 0.158
Learning and retention	-0.10 ± 0.64	0.07 ± 0.38	-0.16 ± 0.71	t=0.875; p = 0.389
Overall cognition	-0.26 ± 0.55	-0.06 ± 0.37	-0.34 ± 0.60	t=1.241; p = 0.225
Note: Benzodiazepines (BZD), Standard deviation (SD).				

Table 1: Cognitive domains in relation with Benzodiazepines treatment.

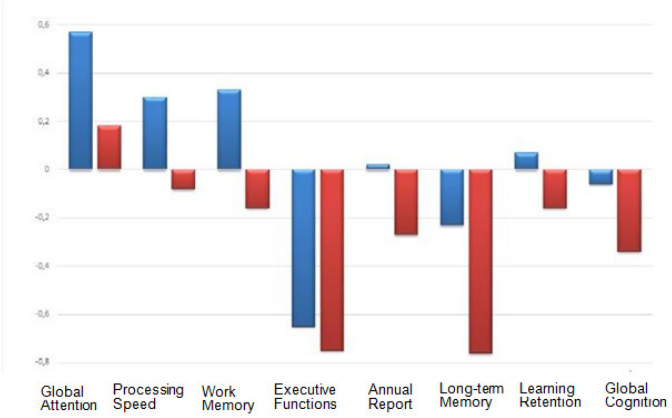

Figure 1 Cognitive Domains with/without Treatment with Benzodiazepine (BZD). Note: (■) No BZD; (■) Yes BZD

Discussion

In relation to the aim of this study, we found that 34.9% of bipolar patients were under Benzodiazepine (BZD) treatment 6 months after the appearance of the disease. This incidence found in our study is similar to the one described in a recent article in which, 35% of patients with affective disorders receive Benzodiazepine (BZD) and which is related with the fact of being treated at the beginning of the disease by non-psychiatric doctors and with a longer duration of untreated disease period [8]. Also, in a study performed in hospitalized patients, 36% released patients had Benzodiazepine (BZD) prescribed in their treatment, which is a risk factor for bipolar disorder [9]. However, this same study showed that the use of Benzodiazepine (BZD) after 3 years of the disease being diagnosed is around 14.7%. In Europe, Sweden recorded an incidence of patients with bipolar disorder under Benzodiazepine (BZD) treatment of 29% [6]. In Spain, 11.4% of the population is under Benzodiazepine (BZD) treatment, especially women, elderly population and patients with mental pathology [10].

In the Basque Country, autonomous region of Spain, it is calculated that more than 10% of the population are under Benzodiazepine (BZD) treatment. Furthermore, in this region, 83% of patient's Benzodiazepine (BZD) therapy has been shown to have duration of at least 6 months, even exceeding 5 years in approximately 26% of the cases. Bearing in mind that the main indications for Benzodiazepine (BZD) are short-term treatment of insomnia and anxiety disorders we can conclude that, in most of the cases, the international guidelines concerning the use and halting of Benzodiazepine (BZD) treatment are not followed correctly, nevertheless, according to the results of this research, in patients diagnosed with bipolar disorder, the doses of Benzodiazepine (BZD) is progressively reduced over the first 3 years of treatment [11].

On the other hand, adverse effects of Benzodiazepine (BZD) on cognition are reported, especially in older patients. Since bipolar disorder is associated with cognitive disorders these patients are particularly vulnerable. In this study, the prescription of Benzodiazepine (BZD) in bipolar patients was limited in most patients [2,12]. Furthermore, it should be noted that no cognitive problems associated with the use of Benzodiazepine (BZD) in the early stages of the disease were detected, except for less overall attention.

The study has certain limitations, for example, the age range that was established (from 18 to 40 years), as it was a study of first bipolar episodes. On the other hand, we do not evaluate possible predictors of greater use of Benzodiazepine (BZD). Finally, it should be mentioned that the patients selected for this study were drawn from cases of entry into an acute hospitalization unit, so the study would not be applicable to patients in outpatient follow-up who do not need hospitalization in a first episode. The study also has important strengths. It is a study conducted at the beginning of the disease and has a thorough cognitive assessment. A three-year follow-up is a sufficiently prolonged period and we should bear in mind that there are no previous studies to analyze the prescription of Benzodiazepine (BZD) in first manic or mixed episodes and its relationship to cognition. In conclusion, this study provides evidence that chronic use of Benzodiazepine (BZD) is limited and does not alter cognitive function, except for overall attention. Protocoled follow-up of care is necessary in bipolar patients receiving Benzodiazepine (BZD).

Declarations

Ethics approval and consent to participate

The Declaration of Helsinki rules were used by our ethics committee in order to approve the design and authorization of this study. Both verbal and written consent to participate were obtained.

Consent for publication

Not applicable.

Availability of data and material

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

Marta Zubia Martin declares having received scholarships from the SEP and aid to attend congresses from Janssen-Cilag and Lundbeck.

Susana Alberich Mesa: no conflict of interest.

Maria Purificación López Peña declares having received scholarships from: Novartis, Janssen and Lundbeck.

Iñaki Zorrilla Martinez declares having given lectures or received scholarships from the following entities: Lundbeck, Angelini, Novartis and Janssen.

Juan Pablo Chart Pascual: no conflicts of interest.

Ana González-Pinto Arrillaga declares having given lectures, advised or received scholarships from the following entities: Janssen-Cilag, Lundbeck, Otsuka, Pfizer, Sanofi-Aventis, Alter, Angelini, Exeltis, Takeda, Spanish Ministry of Health (CIBERSAM) , (Carlos III Institute), Basque Government and the European research framework.

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Authors' contributions

All authors contributed to this manuscript.

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