

Use of Benzodiazepines in Patients With Bipolar Disorder

Marta Zubia Martin (✉ martha15z@hotmail.com)

Osakidetza Servicio Vasco de Salud Comarca Araba <https://orcid.org/0000-0003-2584-9679>

Susana Alberich Mesa

Osakidetza-Basque Health Service: Osakidetza-Servicio Vasco de Salud

Maria Purificación López Peña

Osakidetza-Basque Health Service: Osakidetza-Servicio Vasco de Salud

Iñaki Zorrilla Martínez

Osakidetza-Basque Health Service: Osakidetza-Servicio Vasco de Salud

Juan Pablo Chart Pascual

Osakidetza-Basque Health Service: Osakidetza-Servicio Vasco de Salud

Ana Maria González Pinto

Osakidetza-Basque Health Service: Osakidetza-Servicio Vasco de Salud

Short communication

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Abstract

Background

Benzodiazepines (BZDs) are widely used in patients with bipolar disorder. The aim of this study was to determine chronic use of 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 BZDs in the baseline sample was evaluated at 6 months and for the next 3 years. Cognitive functioning was compared between patients with chronic 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 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 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).

Conclusions

Chronic administration of 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.

Background

Benzodiazepines (BZD) are widely used drugs for the treatment of anxiety, sleep disorders, adjuvant therapy in patients with depression/mania and as muscle relaxants (Preskorn et al. 2015). These drugs are considered effective and safe in short term use; however, their long-term use is associated with adverse health outcomes (Brandt et al. 2017; Clark et al. 2004; Díaz-Gutiérrez et al. 2017).

Clinical guidelines recommend that BZD treatment should be kept as short and at the lowest dosage possible (Preskorn et al. 2015). BDZ are commonly used in patients with bipolar disorder and it should be noted that cognitive disorders are a possible side effect of BZD, and could worsen the prognosis for such patients (Stewart et al. 2005; Wingård et al. 2018).

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 BDZ (Brandt et al. 2017; Clark et al. 2004).

Our aim was to establish the incidence of acute and chronic use of BZDs in patients who suffered a first bipolar episode. In addition, we studied the possible association between long-term BZD 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 (Moran et al. 2016) 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. 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 BDZ at three specific periods of time: Baseline, 6 months and 3 years of follow-up. A duration of 6 months or longer was established to define chronic use of BZD.

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 (\pm 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 BZD 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 BZD 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 BZD 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 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 BZD for 6 months or more (Figure S1).

When comparing BZD intake between each patient visit, 85% ($n = 24$) of the patients who did not take 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 BZD treatment after 6 months ($\chi^2 = 9.443$, $p = 0.002$). Regarding the visits performed at 6 months and 3 years, 90% ($n = 37$) of those who did not take BZD at 6 months, did not do so at the end of follow-up, while in the group that did take BZD at 6 months, 77% ($n = 17$) did not have this treatment at 3 years, there were no significant differences between the two groups ($\chi^2 = 1.967$ $p = 0,161$)

Patients with chronic BZD treatment recorded worse results in all cognitive domains (Table 1), becoming this significant difference in overall attention ($t = 2,481$; $p = 0.020$) (Fig. 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 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 BZD treatment.

Table 1: Cognitive domains in relation with Benzodiazepines treatment.

Variable	Total	No BZD	Yes BZD	Statistics
average \pm SD	(n = 63)	(n = 21)	(n = 42)	
Overall attention	0,29 \pm 0,52	0,57 \pm 0,28	0,18 \pm 0,56	t=2,481; p = 0,020
Processing speed	0,03 \pm 0,74	0,30 \pm 0,55	-0,07 \pm 0,79	t=1,241; p = 0,225
Working Memory	-0,03 \pm 0,75	0,33 \pm 0,59	-0,16 \pm 0,76	t=1,646; p = 0,111
Executive functions	-0,71 \pm 0,42	-0,65 \pm 0,56	-0,75 \pm 0,34	t=0,529; p = 0,603
Short term memory	-0,19 \pm 0,79	0,02 \pm 0,75	-0,27 \pm 0,81	t=0,875; p = 0,389
Long term memory	-0,62 \pm 0,90	-0,23 \pm 0,72	-0,76 \pm 0,93	t=1,450; p = 0,158
Learning and retention	-0,10 \pm 0,64	0,07 \pm 0,38	-0,16 \pm 0,71	t=0,875; p = 0,389
Overall cognition	-0,26 \pm 0,55	-0,06 \pm 0,37	-0,34 \pm 0,60	t=1,241; p = 0,225

BZD, benzodiazepines; **SD**, standard deviation.

Discussion

In relation to the aim of this study, we found that 34.9% of bipolar patients were under 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 (Carlo et al., 2019) in which, 35% of patients with affective disorders receive 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. Also, in a study performed in hospitalized patients, 36% released patients had BZD prescribed in their treatment, which is a risk factor for bipolar disorder (Peters et al., 2015). However, this same study showed that the use of 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 BZD treatment of 29% (Wingård et al. 2018). In Spain, 11.4% of the population is under BZD treatment, especially women, elderly population and patients with mental pathology (Martinez-Cengotitabengoa et al. 2018).

In the Basque Country, autonomous region of Spain, it is calculated that more than 10% of the population are under BZD treatment (Departamento de Salud et al 2020). Furthermore, in this region, 83% of patient's BZD therapy has been shown to have a duration of at least 6 months, even exceeding 5 years in approximately 26% of the cases. (Departamento de Salud et al 2020). Bearing in mind that the main indications for BZD are short-term treatment of insomnia and anxiety disorders (Departamento de Salud et al 2020), we can conclude that, in most of the cases, the international guidelines concerning the use and halting of BZD treatment are not followed correctly, nevertheless, according to the results of this research, in patients diagnosed with bipolar disorder, the dosis of BZD is progressively reduced over the first 3 years of treatment.

On the other hand, adverse effects of BZD on cognition (Brandt et al. 2017) are reported, especially in older patients. Since bipolar disorder is associated with cognitive disorders (González-Ortega et al. 2019), these patients are particularly vulnerable. In this study, the prescription of BZD in bipolar patients was limited in most patients. Furthermore, it should be noted that no cognitive problems associated with the use of 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 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 BZD in first manic or mixed episodes and its relationship to cognition.

In conclusion, this study provides evidence that chronic use of BZD is limited and does not alter cognitive function, except for overall attention. Protocolled follow-up of care is necessary in bipolar patients receiving 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 to have received scholarships from the SEP and aid to attend congresses from Janssen-Cilag y Lundbeck.

-Susana Alberich Mesa: no conflicts of interest

-Maria Purificación López Peña declares to have received scholarships from: Novartis, Janssen y Lundbeck.

-Iñaki Zorrilla Martinez declares to have given conferences or received scholarships from the following entities: Lundbeck, Angelini, Novartis y Janssen.

-Juan Pablo Chart Pascual: no conflicts of interest

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

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Supplementary Files

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