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Substance use and course of bipolar disorder in an inpatient sample

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Introduction. Patients with bipolar disorder (BD) have a comorbid substance use with high frequency. Our study aims to establish a relationship between substance use and BD, in terms of greater diagnostic difficulty, a worse prognosis and changes in pharmacological prescription.

Methods. The sample consisted of 394 subjects over twenty years were hospitalized with a diagnosis of BD in acute psychiatry unit of a general hospital (10.6% of total of 3,704 patients). The medical records were analyzed for demographic, clinical and family group relating to data subjects.

Results. Complete data were obtained from 319 patients. Of these 165 (51.7%) had a history of drug consumption (abuse/dependence). This was more frequent in men (79.7% vs. 34.2%), in patients under 65 years (58.4% vs. 16.7%) and BD type I compared to type II (55% vs. 35%). Consumers substance patients had an age of onset of the disease earlier and more diagnostic difficulties. Regarding treatment, receiving discharge more mood stabilizers and antipsychotics than nonusers, and higher doses of most of them.

Conclusions. The cases of dual pathology were detected in more than half of the sample, being the most serious and poorer prognosis patients, besides presenting a debut earlier disease. BD / substance use association was more common in men and in patients under 65 years.

Keywords: Bipolar Disorder, Substance Use, Dual Diagnosis, Age of Onset, Comorbidity

Actas Esp Psiquiatr 2018;46(5):183-191

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Uso de sustancias y curso del trastorno bipolar en una muestra de pacientes hospitalizados

Introducción. Los pacientes con trastorno bipolar (TB) presentan un consumo de sustancias comórbido con elevada frecuencia. Nuestro estudio pretende establecer una relación entre el consumo de sustancias y el TB, en cuanto a una mayor dificultad diagnóstica, un peor pronóstico y cambios en la prescripción farmacológica.

Métodos. La muestra estuvo compuesta por 394 sujetos que a lo largo de veinte años fueron hospitalizados con un diagnóstico de TB en la unidad de agudos de Psiquiatría de un hospital general (10,6% del total de 3704 pacientes ingresados). Las historias clínicas fueron analizadas para obtener datos demográficos, clínicos y relativos al grupo familiar de los sujetos.

Resultados. Se obtuvieron datos completos de 319 pacientes. De ellos 165 (51,7%) presentaban antecedentes personales de consumo de sustancias (abuso/dependencia). Este fue más frecuente en hombres (79,7% vs. 34,2%), en menores de 65 años (58,4% vs. 16,7%) y en el TB tipo I respecto al II (55% vs. 35%). Los pacientes consumidores de sustancias presentaban una edad de inicio de la enfermedad más precoz así como más dificultades diagnósticas. Respecto al tratamiento, recibían al alta más estabilizadores del estado de ánimo y más antipsicóticos, así como dosis más elevadas de la mayoría de ellos.

Conclusiones. Los casos de patología dual fueron detectados en más de la mitad de la muestra, siendo los más graves y con peor pronóstico, presentando además un debut más temprano de la enfermedad. La asociación TB / consumo de sustancias fue más frecuente en hombres y en menores de 65 años.

Palabras clave: Trastorno Bipolar, Consumo de Sustancias, Patología Dual, Edad de Inicio, Comorbilidad

INTRODUCTION

Bipolar disorder (BD) is a pathology that is accompanied by high rates of Axis I comorbidities such as anxiety disorders^{1,2}, obsessive-compulsive disorder³⁻⁶, panic disorder^{7,8}, eating disorders^{9,10}, impulse control disorder, and attention deficit hyperactivity disorder. Comorbidities of BD also include personality disorders¹¹, especially of clusters B and C, and certain somatic diseases, especially migraines, cardiovascular diseases, and diabetes mellitus. A study by Merikangas (2007) found that 80% of bipolar patients, both type I and type II, presented 3 or more comorbid disorders throughout their lives¹².

Dual pathology is defined as the presence of an addictive and a mental disorder in an individual within a specific period¹³. This type of comorbidity is common as has been found in major epidemiological studies of the general population¹⁴ and in clinical samples¹⁵. In the NESARC (National Epidemiological Survey of Alcohol and Related Conditions) study of 2013, which was based on a large representative US sample (n=43 093), the diagnosis throughout life of any mental disorder was associated with a high prevalence of transition from substance "use" to "substance use disorder", with this association being strongest for tobacco¹⁶. One of the main complications that can occur in bipolar disease, and especially in type I, is its potential association with a comorbid substance consumption. It is estimated that this may occur in about 50% of patients. The Epidemiologic Catchment Area (ECA) study¹⁴ found a higher prevalence of substance abuse in subjects diagnosed with BD (41%) than in the general population. Similar figures were found in the National Comorbidity Survey (NCS) with 46%¹⁷, the Edmonton study with 34%¹⁸, and a 2016 systematic review and meta-analysis of national surveys of general populations with 33%¹⁹. Subjects with a history of substance abuse have a 7-fold greater risk of meeting BD diagnostic criteria²⁰.

Bipolar patients with comorbid substance abuse present a worse course and poorer prognosis of the disease, and this is especially relevant for its rapid detection and its treatment^{4,5,21-26}. Higher comorbidity ratios of substance abuse and dependence have been observed in bipolar I than in bipolar II. A study by Weissman²⁷ found 51% of bipolar type II to have no kind of substance abuse or dependence, as against only 39% of bipolar type I.

In general, bipolar patients are reported to present increased consumption of all substances²⁸. In the particular case of alcohol, large-sample epidemiological studies (ECA, NCS, Edmonton) have found close to 50% of type I bipolar subjects who have a history of alcohol abuse/dependence^{14,17,29}. In clinical samples, the numbers differ considerably but are still high^{30,31}, being greater in men than in women^{25,32-36}. In the ECA study¹⁴, the prevalence of alcohol use

depended on the different psychiatric diagnoses, with type I BD being the most frequent associated mental disorder, followed by type II BD and schizophrenia. Comorbid alcohol abuse can also be a predictor of a less favourable course of BD, with more suicide attempts, more frequent dysphoric mania, more mixed manias and rapid cycles, younger onset, more hospitalizations, slower recovery, poorer adherence to treatment, and worse evolution at 15 years of follow-up relative to patients without alcohol abuse^{5,24,31,34,37-43}. Bipolar patients also more often tend to the abuse of cocaine, other stimulants, and cannabis than controls and subjects with other psychiatric disorders^{31,44,45}, with the association between mood disorders in general and cannabis use being well documented⁴⁶.

Given this context, the objective of the present study was to determine from the data of a sample of hospitalized patients whether there is a relationship between substance use and BD, and, more specifically, whether substance use might affect establishment of the disease's diagnosis, its prognosis, its course, and the patterns of drug prescription.

METHODS

Sample

A retrospective descriptive study was made of cases and controls. The data were obtained from the discharge reports of BD-diagnosed patients admitted to the Psychiatry Brief Hospitalization Unit (BHU) of the *Hospital Infanta Cristina* of Badajoz during the study period of the preceding 21 years, and who met the inclusion criteria. This BHU serves a population of approximately 380 000 inhabitants of the health areas of Badajoz and Zafra-Llerena in Spain's Autonomous Community of Extremadura. Prior to initiating the study, permission was obtained from the Ethics and Research Committee of the Infanta Cristina University Hospital of Badajoz which serves the Badajoz health area.

Methods

The inclusion criteria were:

- a) That the patient had been discharged from the Psychiatry BHU between 1 January 1995 and 30 May 2016.
- b) That, as the main diagnosis in the discharge report of the last admission, the patient had one of the following diagnoses according to DSM-IV-TR⁴⁷ with ICD-10 codes: Bipolar Disorder Type I (F30.x; F31.x); Bipolar Disorder Type II (F31.8); Cyclothymic Disorder (F34.0); Bipolar Disorder Not Otherwise Specified (F31.9); and Schizoaffective Disorder, Bipolar Type (F25.0).

- c) That, as a secondary diagnosis in the discharge report of the last admission, the patient had a diagnosis of substance abuse or dependence according to DSM-IV-TR⁴⁷ with ICD-10 codes (F1x.1 and F1x.2x, respectively). This group would subsequently be compared in the statistical analysis with that of patients who did not have a diagnosis of substance abuse or dependence.

In order to arrive at the diagnoses of the different Axis I pathologies, in the first years of the study the aforementioned Unit used the Composite International Diagnostic Interview, CIDI⁴⁸, as a diagnostic instrument, but it later began to use the structured Mini International Neuropsychiatric Interview (MINI)⁴⁹, version 5.0, because of its brevity of application. Both provide diagnoses of Axis I psychiatric disorders according to DSM-IV and ICD-10 criteria. MINI's validity and reliability have been studied by comparing it with SCID-I and CIDI^{50,51}, the results showing that it scored acceptably high on validity and reliability at the same time as requiring far less time to administer, and that clinicians can use it after only a brief training session. This diagnosis was always reflected in the corresponding discharge report by psychiatrists with experience in the diagnosis and treatment of acute-phase mental disorders. Mental disorders that were not evaluated by the said structured diagnostic interviews, including personality disorders, were explored through the clinical interview.

Of the total of 3704 clinical histories analysed, 394 (10.64%) presented one of the main BD diagnoses of the inclusion criteria. However, for the purposes of the present communication, 75 histories were excluded because either a structured diagnostic interview was not used or the data were incomplete. This left 319 clinical histories.

The data retrieved from these histories were sociodemographic, clinical, diagnostic difficulties, prognoses, and treatment received. Adherence to treatment was described as good or bad according to what was recorded in the medical record from information provided by family, caregivers, other health professionals, and the patients themselves.

To study the predominant polarity, we used the criteria defined by Colom et al. (2006)⁵². This takes predominantly manic polarity to be when at least two-thirds of the episodes meet DSM-IV criteria for a manic or hypomanic episode, and predominantly depressive polarity to be when at least two-thirds of the episodes meet DSM-IV criteria for either a major depressive episode or investigation DSM-IV criteria of a minor depressive episode.

Statistical analyses

The data were retrieved in accordance with a previously created data collection protocol. The different statistical

analyses were carried out using the SPSS version 15 software package⁵³. Subjects were assigned to two groups according to whether or not they had a diagnosis of substance abuse/dependence. In the descriptive analyses, a chi-squared test with Yates correction was used for between-group comparisons of categorical data, and a Student's t-test or an ANOVA for interval data according to whether there were 2 or more than 2 groups, respectively. All statistical analyses were two-tailed, and the significance level was set at $p \leq 0.05$.

RESULTS

Sociodemographic characteristics

The mean age of the sample was 46.0 years (range 12–87 years), 59.9% were women, 61.7% were from rural areas, 66.3% had completed primary education, and 165 (51.7%) had some diagnosis of substance use (abuse/dependence) disorder (SUD) during their life and 154 (48.3%) no such diagnosis.

By substance, 36.1% of the sample had current or past abuse or dependence on tobacco, 28.8% alcohol, 13.1% cannabis, 8% cocaine, 2.2% heroin, 2.9% of synthetic drugs, and 1.9% other substances (caffeine, sedatives or benzodiazepines, hallucinogens, corticosteroids, etc.). For the smokers, the mean number of cigarettes/day consumed was 24.5, with a standard deviation of 13.7.

Variations in clinical aspects according to the existence of SUD

Regarding differences by sex, 79.7% of the men had SUD compared with 34.2% of the women ($p < 0.001$). By age, 58.1% of the subjects of 25 years of age or younger had SUD, 58.4% of those from 26 to 64 years, and 16.7% of those over 65 years of age ($p < 0.001$). The decade of life in which there was the highest percentage of users was from 20 to 30 years of age, with 72.3%. By diagnosis, SUD patients comprised 55% of the type I BD diagnoses, 35% of the type II, 61.5% of the schizoaffective, 48.9% of the not otherwise specified, and 40% of the cyclothymic ($p = 0.185$).

Substance-use-associated diagnostic difficulties and variations in prognosis

Relative to the non-users, BD substance users presented: younger age at last admission (41.31 vs 51.55 years; $p < 0.001$); an earlier age of onset of the disease (25.07 vs 28.18 years; $p = 0.023$); briefer last admission (19.08 vs 22.55 days; $p = 0.064$); and more admissions in our Unit (2.89 vs

2.35; $p=0.06$). With respect to other variables (Tables 1 and 2), more admittances were needed for the diagnosis of BD and there were more previous diagnoses to BD ($p<0.05$).

Drug treatment received at discharge

With regard to the drug treatment received at discharge (Table 3), a mean of 3.30 psychiatric drugs were prescribed for users as against 3.18 for non-users ($p=0.300$), and users received more mood stabilizers and antipsychotics, but fewer antidepressants and hypnotics. Comparing the drugs individually, we found statistically significant differences between users and non-users for the following: lithium (52.7% vs 39.5%; $p=0.018$), olanzapine (38.2% vs 23.0%; $p=0.004$), quetiapine (23.6% vs 12.5%; $p=0.010$), haloperidol (8.5% vs 18.4%; $p=0.009$), sertraline (0.6% vs 3.9%; $p=0.043$), and nortriptyline (0% vs 3.3%; $p=0.019$). With regard to the doses received (Table 4), the substance users received higher doses of all the stabilizers and most of the antipsychotics and antidepressants.

There was poor adherence to the treatment in 48.4% of the users as against 22.3% of the non-users ($p<0.001$).

DISCUSSION

Of the BD patients admitted to our acute care unit, 51.7% presented SUD during their life. This proportion is somewhat higher than that reported in epidemiological studies^{14,17-19,54}, but lower than the 72% found with other samples of hospitalized patients⁵⁵. Higher rates of comorbid SUD have been reported for Bipolar Type I than for Bipolar Type II^{3,27}, with values in the range 45%-60% for the former and 30%-50% for the latter. These figures are coherent with the present findings. We found the diagnostic subgroup with the highest SUD comorbidity rate to be bipolar type schizoaffective disorder, as also has already been described in the literature⁵⁶. With the consumption separated between legal (alcohol and/or tobacco) and illegal (the rest, including with the additional use of alcohol and/or tobacco), the proportions of patients with these comorbidities were 33.9% and 17.9%, respectively. These figure are practically equal to those of the meta-analysis of Hunt et al. (2016)¹⁹. This found an overall 17% of illicit substance use, although its grouping of studies together did not take into account that the types of substance use can differ widely between countries and over time.

With respect to alcohol, our proportion (28.8%) was lower than the values reported in large-sample epidemiological studies – ECA: 46%¹⁴; Edmonton Study: 45%²⁹; NCS: 64%¹⁷ – but higher than that in Hunt et al.'s systematic review and meta-analysis – 24%¹⁹. A recent study of outpa-

Table 1	Psychiatric antecedents and differences between user and non-user bipolar disorder patients		
	User BD	Non-user BD	p
Number of admittances up to BD diagnosis	1.50	1.23	0.004
Total of days hospitalized in all admittances in Badajoz	59.78	59.24	0.956
Average stay total admittances in Badajoz	19.33	21.82	0.119
Total number of admittances in all centres	4.03	4.15	0.805
Number of previous diagnoses	1.14	0.86	0.021
% who had received a previous diagnosis	64.5	64.9	0.948
BD: bipolar disorder			

tient psychiatric patients in Spain's Autonomous Communities of Extremadura and Catalonia³⁵ used the CAGE questionnaire to screen for alcohol use. It found 45.2% of the BD patients to screen as positive, with this being defined as a score of 1 or more. The percentage was greater in men and in patients younger than 60. Other drugs described in the literature as being frequently associated with BD, such as cannabis and cocaine,^{28,45,46,57} also presented this association in our sample.

González-Pinto et al. (1998)⁵⁸ compared the proportion of smokers (both occasional and daily consumers) in BD patients with that in a healthy population, applying the Fagerstrom test of nicotine dependence. The results suggested a greater frequency in the BD patients, with the difference being statistically significant in the case of men. We found more than a third of the BD patients to be smokers, a proportion that is higher both for women and especially for men than reported in other studies of healthy samples of the Extremadura population^{59,60}.

With regard to differences by sex, the literature on BD patients reports more frequent substance use in men than in women^{25,32-36,44,61}. This is so for each substance separately as well as overall, and for both sexes the figures are higher than in the general population. In our case, we found large differences in SUD between men and women, with the frequency reaching a level in men (very close to 80%) that is remarkable, being especially high in the youngest age group. That is why, given its high prevalence in young male bipolar

Table 2 Clinical variables which showed statistically significant differences between user and non-user bipolar disorder patients

	User BD		Non-user BD		P
	N	%	N	%	
Admitted for behavioural alteration	78	47.3	40	26.3	<0.001
Admitted because of a court order	9	5.5	0	0	0.003
Secondary clinical judgement of cognitive impairment	2	1.2	9	5.8	0.023
Secondary clinical judgement of personality disorder	19	11.5	7	4.5	0.023
Previous diagnosis of schizophrenia	13	8.4	2	1.5	0.010
Previous diagnosis of schizophreniform disorder	8	5.2	1	0.8	0.034
Previous diagnosis of depression	37	23.9	54	41.2	0.004
Previous diagnosis of substance abuse/dependence	23	14.8	0	0	<0.001
Previous diagnosis of personality disorder	24	15.5	7	5.3	0.006
Axis IV problem	26	16.4	9	6.5	0.009
Predominantly manic polarity	110	82.1	75	59.5	<0.001
Predominantly depressive polarity	24	17.9	51	40.5	<0.001
General family psychiatric antecedents	112	77.8	82	63.6	0.010
Family substance use antecedents	33	22.9	14	11.0	0.010
3 or more personal somatic antecedents	47	28.8	58	39.5	0.048

BD: bipolar disorder

patients, it is necessary to explore possible SUD in this subgroup for the better treatment and evolution of their bipolar pathology.

BD patients with comorbid substance abuse present a poorer course and prognosis of the disease, with more hospitalizations, more mixed manias and rapid cycles, slower recovery, worse adherence to treatment, an earlier age of onset, and more suicidal ideation^{4,5,21-26,40}. These conclusions in the literature are similar to the findings of the present study. Our BD patients with substance use were the most serious and had the worst prognosis. They had more admissions in the Badajoz BHU than non-users, more psychosocial problems, poorer adherence to treatment, and required a greater number of drugs (especially mood stabilizers and antipsychotics) and higher doses, all of which reflects the difficulty in managing these patients. In addition, as is also referred to in the aforementioned literature, they also had an earlier age of onset of the disease, which could lead one to think that the substance use advanced the age of presenta-

tion of the disease and could even have been its cause. It has been considered²⁸ that there are substances which, while they can induce pathological affective states, can also help regulate short-term negative emotional states, although, long term, they have a more damaging effect and are also substances whose consumption is increased during the manic phases due to the state of exalted mood and disinhibition present in those episodes.

With respect to the drug treatment received at discharge, a study with certain methodological similarities to ours was carried out in Madrid on 225 BD patients admitted in their last manic episode⁶². Only the treatment at discharge was analysed, finding differences in the total daily doses of antipsychotics and biperiden. This is similar to our results, although in our study we found that BD patients with SUD also received more stabilizers and antipsychotics, but fewer antidepressants and hypnotics, and that most drugs were prescribed at higher doses. It has to be taken into account as

Table 3	Drug treatment received at discharge and differences between user and non-user bipolar disorder patients		
Pharmacological treatment at discharge	User BD	Non-user BD	p
Number of psychiatric drugs	3.30	3.18	0.300
Number of mood stabilizers	1.13	0.92	0.003
Number of antipsychotics	1.26	1.13	0.076
Number of antidepressants	0.16	0.30	0.016
Number of benzodiazepines	0.59	0.64	0.367
Number of hypnotics	0.03	0.11	0.017
% with mood stabilizers	87.9	77.0	0.010
% with antipsychotics	92.7	85.5	0.038
% with antidepressants	12.7	27.0	0.001
% with benzodiazepines	58.8	63.2	0.426
% with hypnotics	3.6	9.9	0.026
BD: bipolar disorder			

well that we did not only analyse admissions in the manic phase.

Predominantly manic polarity has been associated with higher rates of substance abuse⁶³. As the disease progresses, the depressive phases begin to predominate over the manic⁶⁴. These may be the reasons why a greater proportion of our BD patients with associated SUD had a predominantly manic polarity than the non-users since the users were on average much younger. This fact may also be a partial explanation of why our BD patients with SUD received more antipsychotics and fewer antidepressants than the non-users. This is coherent with the findings of Colom et al. (2006)⁵² whose patients with manic polarity received more antipsychotics, and those with depressive polarity more antidepressants. González Pinto et al. (2010)⁶⁵ found slightly more frequent alcohol abuse (43.2% vs 35.3%) and other substances abuse (13.6% vs 9.8%) in their predominantly manic polarity group relative to the predominantly depressive polarity group. Nevertheless, they found that, at the 10-year follow-up, the frequency of both alcohol and other substances abuse fell significantly only in the predominantly manic polarity group.

The diagnosis of bipolar disorder is often complicated by its sharing symptoms with other psychiatric diseases. This

Table 4		Doses (mg) of the main treatment drugs in the study (used for more than 10 patients of each group), and differences between user and non-user bipolar disorder patients			
	User BD		Non-user BD		p
	N	Average dose	N	Average dose	
Lithium	87	1047.13	60	925.00	0.018
Valproic acid	42	1333.33	39	1185.89	0.122
Oxcarbazepine	19	1294.73	10	990.00	0.062
Lamotrigine	10	220.00	11	213.64	0.936
Carbamazepine	16	737.50	13	638.46	0.401
Olanzapine	63	24.36	35	17.14	0.001
Risperidone	28	5.18	34	4.26	0.227
Quetiapine	39	717.95	19	463.16	0.001
Haloperidol	14	4.75	28	4.89	0.896
Levomepromazine	27	70.37	24	56.77	0.345
Lorazepam	30	5.29	30	3.73	0.065
Clonazepam	47	3.37	53	3.17	0.554
Biperiden	11	4.18	11	2.91	0.030
BD: bipolar disorder					

can lead to a delay in diagnosis which in turn has been associated with a poorer response to treatment⁶⁶. For example, an epidemiological study of BD in Spain⁶⁷ found the mean time between the onset of the disease and its diagnosis to be 5.8 years, and that 52.3% of the patients had previously received some other psychiatric diagnosis. Another study⁶⁸ found an even greater diagnostic delay of 9.3 years. Substance use could act as a factor to make the diagnosis of BD even harder since these patients in our sample had more previous psychiatric diagnoses (especially of psychotic disorders, personality disorders, and substance abuse/dependence) and more admittances before the BD diagnosis was reached.

Since the present work was a case-control study that collected information acquired over time, it has the advantage of allowing new hypotheses to be generated and multiple risk factors to be studied simultaneously. It has, however, the limitations inherent to this type of retrospective study. Since the clinical histories were collected by several different psychiatrists over a very long period, there might be a bias due to differences between observers despite a semi-structured interview having been used. We also found that there were missing data in some medical records, especially the older ones, and that in some no use was made of any diagnostic questionnaire, but that diagnosis was based on only a clinical interview, for which reason 75 of the original 394 histories were discarded. Despite this, we consider that one of the strengths of the present study is its moderately large sample size.

Our study provides new data and confirms some previous data on the effect that substance use can have on the course of BD. It seems evident from the analysis of the sample of patients admitted over a period of more than twenty years that a comorbid diagnosis of substance use worsens the prognosis of BD since it is associated with a greater number of admissions and higher doses of psychotropic drugs, as well as being associated with poorer adherence to treatment and greater psychosocial problems. Substance use also seems to be related to earlier onset of the disease and to greater difficulties in its diagnosis since those patients receive more previous psychiatric diagnoses. These negative consequences of substance use should lead to a systematic and meticulous exploration of the associated consumption of substances in all patients with a possible diagnosis of BD with a view to minimizing the negative effects that have been described.

As a final conclusion, we would note that the cases of dual pathology (detected in more than half of our sample and especially frequent in men and in those under 65 years in age) were the most serious, with worse prognosis, more difficult diagnosis, and an earlier onset of the disease.

ACKNOWLEDGEMENTS

The authors are grateful to all the psychiatrists who collaborated in the collection of data over such a long period of time, and who made such a large sample of participants possible.

CONFLICT OF INTERESTS

The authors declare that they have no conflicts of interest nor have they received any type of financing for the preparation of this article..

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