Comparison of psychodrug prescription patterns in patients diagnosed with bipolar disorder and addiction

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Objective. To describe if there are differences in the prescription of psychodrug at discharge between bipolar disorder patients with or without addiction.

Methods. We review all the psychotropic drugs dispensed to inpatients of a brief hospitalization psychiatric unit diagnosed as having bipolar disorder at time of discharge. We recluted 225 patients over 18 years old on their last manic episode, between the year 2000 and 2010. We classify them according to the comorbid presence or not of a substance abuse or dependence disorder.

Results. Prevalence of addiction was 24%. We found no differences between groups in the number of psychotropic drugs prescribed at discharge. The prescription pattern of mood stabilizers and benzodiazepines was similar in both groups. We detect differences in the total daily dose of antipsychotic, expressed as risperidone equivalents (5.86 ± 4.62 mg in addictions group versus 4.67 ± 3.20 mg in control group, p=0.042) and in the total daily dose of biperideno (4.80 ± 1.78 mg in addictions group versus 3.20 ± 1.03 mg in the control group, p=0.044).

Conclusions. Contrary to our expectations, both groups were similar in psychopharmacological prescription patterns at discharge. However, those patients with substance abuse disorder had higher doses of antipsychotics and higher dose biperiden at discharge.

Keywords: Bipolar disorder, Comorbidity, Mania, Alcoholism, Addiction, Psychoactive drugs

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Comparación de los patrones de prescripción farmacológica en pacientes diagnosticados de trastorno bipolar y adicción

Objetivo. Analizar si existen diferencias en la prescripción de psicofármacos en el momento del alta hospitalaria entre los pacientes con trastorno bipolar con o sin adicción.

Métodos. Revisamos todos los psicofármacos dispensados en el momento del alta a todos los pacientes con diagnóstico de trastorno bipolar de una unidad psiquiátrica de hospitalización breve. Seleccionamos a 225 pacientes mayores de 18 años en su último episodio maníaco, entre los años 2000 y 2010. Los clasificamos de acuerdo a la presencia o ausencia de un diagnóstico comórbido en adicciones.

Resultados. La prevalencia de adicciones fue del 24%. No encontramos diferencias entre grupos en cuanto al número de psicofármacos prescritos al alta. El patrón de prescripción de los estabilizadores del ánimo y las benzodiacepinas fue similar en ambos grupos. Detectamos diferencias en cuanto a la dosis diaria total de antipsicóticos expresada como equivalentes de risperidona (5.86 ± 4.62 mg en el grupo de adicciones frente a 4.67 ± 3.20 mg en el grupo control, p=0.042) y en cuanto a las dosis diaria total de biperideno (4.80 ± 1.78 mg en el grupo de adicciones frente a 3.20 ± 1.03 mg en el grupo control, p=0.044).

Conclusiones. Contrariamente a nuestras expectativas, ambos grupos presentaron similares patrones de prescripción psicofarmacológicos al alta. Sin embargo, los pacientes con diagnóstico en adicción tenían dosis más elevadas de antipsicóticos (expresadas como dosis equivalente de risperidona) y dosis superiores de biperideno al alta, respecto a las dosis utilizadas por el grupo control.

Palabras clave: Trastorno bipolar, Comorbilidad, Manía, Alcoholismo, Adicción, Psicofármacos

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INTRODUCTION

A clear association between bipolar disorder and abuse disorders and/or substance dependence disorder has been revealed by several large epidemiologic studies[1-3].

Some evidences show a prevalence in addiction higher than 61% in bipolar patients, they have 10 times more likely to have a disorder alcohol dependence, and up to 8 times more likely to have other abuse or substance dependence, regarding the general population[1].

These studies also show that this comorbidity is more common than bipolar disorder with other psychiatric disorders such as obsessive compulsive disorder (21%), panic disorder (20.8%), social phobia (16.47%) and disorders eating disorders (>10%)[4,5.]

Some authors describe certain degrees of overlap in the pathogenetic mechanisms of both disorders, being a common phenomenon called "neuronal kindling" and consisting of an acceleration of the course of the disease when a certain number of events occurs, succeeding episodes more frequently and shortening the period of symptomatic remission between episodes. This phenomenon has been described also in: cocaine use disorder, alcohol withdrawal, unipolar and bipolar depression

This relationship is not only important because of its high prevalence, but because it has been associated with an earlier debut of bipolar disease, more frequent hospitalizations by emotional decompensation reasons, a higher percentage of rapid cycling patients (subgroup of disorder bipolar with worse prognosis) and the presence of mixed states (in coexisting depressive and manic mood symptoms)[7].

Studies in comorbid alcoholism suggest less adherence to treatment[8], increase of health spending[9], increase of medical comorbidity, impaire in cognitive functions[10,11] and an increase of suicide risk[12]. Other findings show that alcoholism in bipolar patients is associated with more severe manic and depressive episodes, with a marked increase in impulsivity and presence of violent behaviors.[13]

Therefore, we consider this comorbidity is a serious public health problem, and yet there is little information on the pharmacological management of these situations where both disorders coexist, since patients with addictions most often are excluded from clinical drug trials.

The main clinical practice guidelines recommend the use of lithium or valproate to treat hipomanic episodes of bipolar disorder, and adding an antipsychotic for handling severe episodes[14,15].

Regarding the phenomenon of neuronal kindeling, some authors suggest that drugs with antiepileptic activity such as carbamazepine and valproic acid would be more suitable for dual patients because it would give greater stability to the neuronal membrane, they prevent events, for example like seizures during alcohol withdrawal, relegating the lithium to the classical mania treatment. Lithium monotherapy has not proven helpful in reducing alcohol intake and also not shown effective in dysphoric mania, or mixed episodes in patients with rapid cycling, which generally correspond to the profile of patients with bipolar disorder and alcoholism[16-20].

Salloum published the benefits of adding valproic acid to patients with bipolar disorder and alcoholism treated with lithium, they achieved a reduction in the consumption of alcohol[16]. Carbamazepine has also shown efficacy in the treatment of manic episode and on reducing the consumption alcohol[17,18]; antiepileptic topiramate has also shown efficacy in reducing alcohol intake[19].

These contradictions described in the medical literature are the main justification for conducting our study: analyze patterns psychopharmacological prescription at the time of hospital discharge in order to describe what happens in routine clinical practice in our environment. Are there differences in the prescription pattern of patients with bipolar affective disorder with or without comorbid addiction?

MATERIALS AND METHODS

Objectives of the study

Determine whether there are differences in main variables related to the prescription of psychoactive drugs at the time of hospital discharge among bipolar disorder patients with or without comorbid addiction. We select the time of discharge because we understand that at that time symptomatic remission has been acquired.

Study design

This is a retrospective observational study using data from administrative documents provided by the admission department of Dr. Rodríguez Lafora Hospital; and pharmacological and clinical variables collected by the team of psychiatrists and clinical psychologists of the hospital. We create a database from the diagnostic codes used at the time of discharge of patients with bipolar affective disorder admitted to their last manic episode in our brief hospitalization unit. We use the codes of the International Statistical Classification of Diseases, Ninth Revision (ICD-9)[21], to make this selection. We included patients admitted between January 2000 and December 2010.

The patients included in the study met ICD-9 criteria for bipolar affective disorder. We classified as the addictions group those bipolar disorder patients and ICD-9 criteria of abuse disorder and/or dependency for at least one of the following substances: alcohol, cannabis, cocaine, amphetamines, ecstasy, hallucinogens and opiates.

The election of last manic episode

We chose the last manic episode because bipolar disorder is an entity that initially can be confused with many other psychiatric diagnoses such as unipolar depression, personality disorder and schizophrenia in the early years of disease progression, including even the first 10 years, causing a delay in the diagnose.

Sample

We included all patients with bipolar affective disorder admitted by manic episode or mixed episode in the period 2000-2010 in brief hospitalization unit of Dr. Rodríguez Lafora, Madrid Hospital. The selection of patients was conducted from an initial data base provided by the admission department of hospital. That base included a total of 380 patients, the inclusion criteria was an ICD-9 diagnostic code 296 at discharge (manic or mixed episode).

Exclusion criteria

We excluded those bipolar disorder patients without manic episodes during that period (ICD-9 codes 296.3) and those patients with organic psychoses (ICD-9 290-294). We obtained a final sample of 225 patients with bipolar disorder, men and women, all over 18 years.

Selected variables

The main socio-demographic variables were: age (expressed as the mean and standard deviation) and gender (male, female).

We observe the following clinical variables: lenght of the bipolar disorder and the presence or absence of a comorbid diagnosis in addiction during the last manic episode, the diagnosis was obtained through clinical assessment performed during admission by the reference psychiatrist.

Psychopharmacological variables: we recorded these variables at the time of patient discharge: number of psychoactive drugs prescribed at the time of discharge, number of mood stabilizers at the time of discharge, percentage of patients treated with each of mood stabilizers and the daily dose of each mood stabilizer expressed in milligrams (mg).

Number of antipsychotics at the time of discharge, percentage of patients treated with each antipsychotic and the daily dose of each antipsychotic, all them expressed as equivalent of the risperidone antipsychotic (we calculated the equivalencies using some references[22-24], this transformation let us do comparisons between groups), prescription of depot antipsychotics at discharge (yes/no).

Number of benzodiazepines at discharge time, percentage of patients treated with each benzodiazepine, the daily dose of benzodiazepines expressed as equivalents of lorazepam in mg (we calculated the equivalencies using some references[22], this transformation let us to do comparisons between groups).

We collected the daily dose of biperiden, expressed in mg, at discharge time.

Also recorded the number of times every psychoactive drug was administered throughout the day to do comparisons between groups.

Data analysis: statistical method

We employed a frequency analysis regarding qualitative and quantitative variables. We expressed the qualitative variables as proportions and quantitative variables using the mean ± standard deviation.

We used chi-square statistic to do comparisons between two cualitative variables (comparisons between variables with two categories), we applied this type of analysis to do comparisons between types of mood stabilizers, antipsychotics and benzodiazepines most frequently prescribed; and an ANOVA test to do comparisons between one cualitative variable and one quantitative one.

We used the 20.0 version of SPSS program to do the statistical analysis.

Ethics

We used a special code, different to the personal one, so data identification has been confidential during all the study.

This procedure is subject to the Law 15/1999 on protection of personal data of 13 December.

The study procedures are according to the Ethics International Declaration of Helsinki (Edinburgh, 2000), and ac-

cording to WHO recommendations and the Ethics Code. The Ethics Committee of Clinical Research from the University Hospital La Paz in Madrid approved the study protocol.

RESULTS

The prevalence of comorbidity in bipolar patients and addiction was 24%. The main epidemiological variables are reflected in table 1.

There is a tendency to a less evolution in time of bipolar disease in the dual group, although the differences found were not statistically significant. (11.97 ± 8.66 years of evolution of bipolar disorder versus 15.57 ± 12.65 years, p=0.073).

The number of psychoactive drugs at discharge was of 3.02 ± 1.17 in the addiction group versus 3.06 ± 1.05 in the control group (p=0.813).

The main psychopharmacological variables related to the prescription of mood stabilizers based on the presence or absence of addiction criteria in the last manic episode are set out in table 2.

Table 1 Main demographic characteristics of our sample

Sociodemografic data	Adicction Group	Control Group	Total
	Proportion (%) o Average ± Standard Deviation		
Men	30 (56)	67 (39)	97
Women	24 (44)	104 (61)	128
Age (years)	39 ± 12	48 ± 15	225

There were no differences between groups regarding the number of daily administrations of each of the different types of mood stabilizers, the average was two times a day.

Lithium and valproic were the mood stabilizers most prescribed in both groups of bipolar patients. We performed a statistical analysis of square Chi, reflected in table 3, in order to establish whether there was any preference in drug prescribing these mood stabilizers, depending on the presence or not of duality.

Table 2 Number of mood stabilizers and daily dose of each one, expressed in milligrammes

Mood Stabilizers		Last Manic Episode		Total	P value
		Addiction Group	Control Group		
		Percentage (%) or Mean ± Standard Deviation			
Number of mood stabilizers at discharge		0.87 ± 0.51	1.07 ± 0.59		
	Total	54	170	224	0.023
Daily dose of lithium (mg)		1073.68 ± 284.49	959.21 ± 337.41	95	
	Total	19	76	160	0.177
Daily dose of valproic (mg)		1340.90 ± 293.84	1456.87 ± 1091.41		
	Total	22	80	102	0.624
Daily dose of carbamazepine (mg)		700.00 ± 141.42	480.00 ± 109.54		
	Total	2	5	7	0.074
Daily dose of oxcarbazepine (mg)		750.00 ± 212.13	1166.67 ± 484.76		
	Total	2	9	11	0.279
Daily dose of lamotrigine (mg)			218.75 ± 84.25		
	Total	0	8	8	
Daily dose of topiramate (mg)		400.00	200.00		
	Total	1	1	2	

Figure 1 shows the frequency distribution of the different types of mood stabilizers prescribed in our sample, based on the presence or absence of addiction criteria in the last manic episode.

The main variables related to prescribing antipsychotics, based on the presence or absence of addiction criteria in the last manic episode are reflected in table 4. This table includes a Chi square statistical analysis between the dicotomic variable "presence of depot antipsychotics at discharge" (yes/no) and the dicotomic variable "presence of addiction criteria in the last manic episode".

Figure 2 shows the frequency distribution of the different types of antipsychotics prescribed in our sample, based on the presence or absence of addiction criteria in the last manic episode. We compared antipsychotics two by two and we did not find any differences between the different types of antipsychotics and the presence or absence of a diagnosis in addiction.

The main variables related to the prescription of benzodiazepines, based on the presence or absence of addiction criteria in the last manic episode, are summarized in table 5.

Figure 3 shows the distribution of the frequency of different types of benzodiazepine prescribed in our sample, based on the presence or absence of addiction criteria in the last manic episode. We compared benzodiazepines two by two and we did not find any differences between the different types of benzodiazepines and the presence or absence of a diagnosis in addiction.

The average total daily dose of biperiden was of 4.80 ± 1.78 mg in the addiction group versus 3.20 ± 1.03 mg in the control group, p=0.044. We found no differences between groups regarding the number of daily administrations of biperiden, the average was 1 once a day.

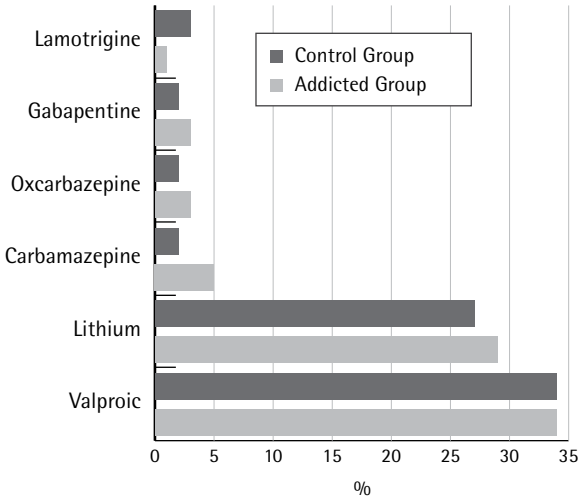

Figure 1 — *Main types of mood stabilizers based on the presence or absence of criteria for addiction during the last manic episode*

DISCUSSION

The medical literature describes difficulties in the therapeutic management of dual bipolar patients: sometimes in relation to the presence of symptoms more severe or to the presence of mixed episodes, agitation and violent behavior, sometimes in relation to the presence of treatment resistance or poor adherence, all them reveal a major health problem. However, the findings of our study indicate that duality in bipolar patients was not associated with different patterns of psychopharmacological prescription, although the addiction group required higher dose of antipsychotics and biperiden significantly than the control group.

Table 3 — **Results of Analysis Chi square type of mood stabilizer (lithium, valproic) versus presence of diagnostic criteria for addiction in the last manic episode**

Type of mood Stabilizer	Last Manic Episode		Total	P value
	Control Group	Grupo sin adicciones		
	Percentage (%)			
Lithium	17 (46)	58 (47)	75	1.000
Valproic	20 (54)	65 (53)	85	
Total	37	123	160	0.177

Table 4 Main variables related to antipsychotics

Antipsychotics		Last Manic Episode		Total	P value
		Addiction Group	Control Group		
		Percentage (%) or Mean ± Standard Deviation			
Average number of antipsychotics at discharge		1.12 ± 0.47	1.10 ± 0.44		
	Total	54	170	224	0.739
Daily dose of antipsychotic, expressed as equivalents of risperidone (mg)		5.86 ± 4.62	4.67 ± 3.20		
	Total	50	156	206	0.042
Prescription of depot antipsychotics at discharge					
	Sí	4 (8)	5 (3)		
	No	47 (92)	158 (97)		
	Total	51	163	214	0.222
Number of daily administrations of antipsychotics		1.84 ± 0.84	1.73 ± 0.81		
	Total	51	162	213	0.401

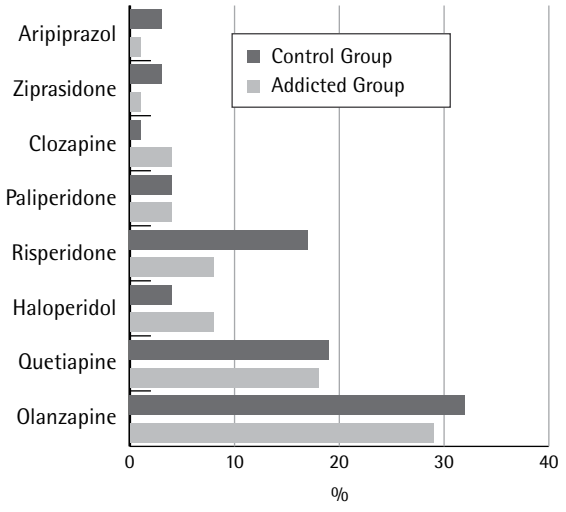

Figure 2 *Main types of antipsychotics prescribed in our sample based on the presence or absence of diagnostic criteria for addiction in the last manic episode*

The twenty four percent of patients with bipolar disorder in our sample met criteria for abuse disorder or substance dependence in the last manic episode, according to ICD-9 criteria. This finding in our sample is lower than the prevalence in other samples such as F Cassidy et al. (39.3%)[25], using diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM IIIR), reason that could justify the differences found. Despite our lower prevalence, study reveals that 1 in 4 bipolar patients have an addiction problem associated, so we consider important to do a comprehensive assessment of information on substance use in all patients diagnosed with bipolar disorder.

The average of psychoactive drugs prescribed at discharge was 3 in both groups, mainly the combination of one antipsychotic plus one mood stabilizer plus one benzodiazepine. The patterns described in the results are consistent with those described in the main clinical practice guidelines for the management of the disorder bipolar[14,15], barely able to define nuances different in the treatment of dual bipolar patients. Breaking down the various components of this polypharmacy we have found:

Antipsychotic

Although the average number of antipsychotics prescribed at hospital discharge in both groups was 1, we found a higher dosage of antipsychotic in the addiction group, however doses remained within the dose range recommended in the label of the psychoactive drug. We attribute these dosage differences to the presence of greater clinical severity present in patients with addiction, evaluated through the administration of the Clinical Global Impression

Table 5 Main variables related to the prescription of benzodiazepines and their distribution based on the presence or absence of criteria for addiction in the last manic episode

Benzodiazepines		Last Manic Episode		Total	P value
		Addiction Group	Control Group		
		Percentage (%) or Mean ± Standard Deviation			
Average number of benzodiazepines at dicharge		0.81 ± 0.64	0.69 ± 0.58		
	Total	54	170	224	0.180
Daily dose of benzodiazepine expressed as equivalents of lorazepam (mg)		2.40 ± 2.47	2.01 ± 2.27		
	Total	40	105	145	0.372
Number of daily administrations of benzodiazepine		2.02 ± 0.99	1.82 ± 0.93		
	Total	40	105	145	0.269

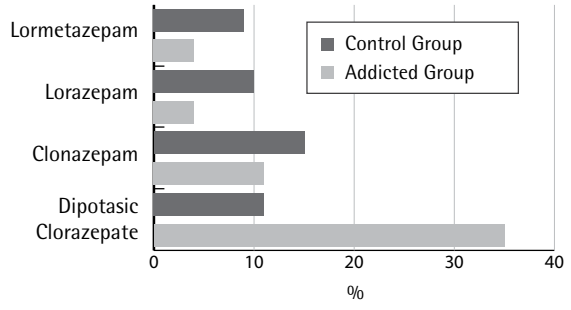

Figure 3 *Main types of benzodiazepines prescribed in our sample based on the presence or absence of diagnostic criteria for addiction in the last manic episode*

scale at the time of admission and discharge (we published this data in an European International Congress)[26].

The atypical ones were antipsychotics most prescribed in both groups, those with a sedative profile of side effects as olanzapine and quetiapine were the most employed. The use of classical antipsychotics, especially haloperidol, was the more prescribed in the addiction group, these psychoactive drugs, although it has a profile of adverse safety (causing extrapyramidal symptoms: tremor, rigidity, akathisia, hypogonadism and galactorrhea), remains highly used in habitual clinical practice because they have an incisive efficacy on clinical patient with psychotic disorder, their use is usually reserved for situations where the clinic is steeper, with the presence of agitation or violent behavior, characteristics that are often present in patients with addiction.

Clozapine, due to their other anticraving property, is typically used in the dual american patients[27], however, in our sample was scarcely employed. In our country, clozapine is a psychoactive drug with a very restricted indications: resistant schizophrenia, because it can cause agranulocytosis so their prescription requires close monitoring of blood count of patients as a prophylactic measure.

We found no differences between groups regarding the number of daily administrations.

Finally, contrary to the expected, the frequency of prescription of depot antipsychotics was low, but we found differences in the percentage of prescription between groups. This curious finding could be explained by the presence of psychoeducational groups conducted during the final stages of hospital admission and which aim, among other objectives, improving the awareness disease in patients with bipolar disorder and the adherence to the treatment.

Mood stabilizer

We believe that the choice of mood stabilizer has a major role in polypharmacy at discharge, since it is likely a progressive supression of antipsychotic and benzodiazepine in outpatient, while the remission of manic symptoms persists, and the mood stabilizer would remain the psychoactive drug during the euthymic phase.

Regarding the distribution of mood stabilizers: lithium and valproic were the most prescribed, we found no differences in distribution by groups, nor as to the total daily dose or the number of administrations per day. These

findings are consistent with the ausence of any type of recomendation in the clinical practice guidelines in relation with the choice of one or the other.

However, we join the opinion that the psychoactive drugs with anti-kindeling effect[16-20] would have the added benefit of reducing the craving for alcohol and other drugs, which could delay and even reduce the number of relapses in abuse substances in dual patients. We consider necessary long-term observational studies to determine whether there are differences in the number of relapses and hospitalizations for psychiatric cause among those dual bipolar patients lithium-treated compared to those treated with anti-kindeling drugs.

Benzodiazepines

We found no significant differences between groups with respect to: the average number of prescribed benzodiazepines, the maximum daily dose of benzodiazepines, we found no differences regarding the number of administrations per day. Regarding the type of benzodiazepine used in the addiction group, we should mention a high prescription of clorazepate dipotassium, benzodiazepine with a long half-life and with significant potential of abuse. Therefore it is important a close follow-up outpatient during the first weeks after discharge, in order to do a gradual withdrawal of benzodiazepines avoiding the possible occurrence of symptoms resulting from withdrawal.

Biperiden

Congruent with a greater need for antipsychotics dose, the dual patients required higher dose of anticholinergic to counter extrapyramidal side effects. It is also important tight control of this type of psychoactive drugs because they have some potential for abuse that should be considered in the comprehensive approach to the dual patients[28].

Although our findings are limited by the small sample size, represent the clinical practice of health areas 4 and 5 of Madrid. Overall our study confirms that there are no significant differences in the pharmacological treatment of manic episode in patients with bipolar disorder, independent of comorbidity in addictions.

We consider important the publication of this finding: on the one hand to reassure clinicians and we believe that, despite the limited information regarding the psychopharmacological approach manic episode in dual populations, following the recommendations of major clinical practice guidelines of bipolar disorder, they are doing a correct therapeutic approach; and secondly to encourage the completion and publication of most observational researchs in order to get an improvement of the approach.

LIMITATIONS

The main limitations of our study were those derived from the selected design type: observational, retrospective, the existence of reporting biases and potential confounders are possible.

Our study mainly includes patients with recurrent affective episodes, it is expected that most of them were treated previously. This factor was not considered in this article, so we can not determine to what extent this variable could contribute to the prescription of psychotropic drugs during admission.

RECOMMENDATIONS

The main advantage of our study is its strong naturalistic character: we analyze patterns of psychopharmacological treatment in the usual clinical routine for treatment of manic episode in patients with bipolar disorder and compared with a subgroup of patients with addiction. We believe that the information contained in this paper, can support psychiatrists about prescription patterns in patients with dual bipolar disorder, remembering that these patients are often excluded from clinical trial and even the economic and temporal difficulties involved in doing a similar design in a prospective sense.

CONCLUSIONS

Both groups were similar with respect to prescription pattern at the time of hospital discharge. However, patients with dual bipolar disorder had higher doses of antipsychotics and biperiden to achieve symptomatic remission. In both groups olanzapine was the most prescribed antipsychotic. Interestingly haloperidol, classic antipsychotic, was highly prescribed in case of addiction. Although clozapine has a good anticraving profile it was little prescribed.

There was a tendency in psychiatrists for prescribing benzodiazepines with a long half-life in the addiction group, although these have shown high potential for abuse.

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