Polypharmacy and suicide attempts in bipolar disorder

Polifarmácia e tentativas de suicídio no transtorno bipolar

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Abstract
Objective: The aim of this study was to assess the association between suicide attempts and the use of multiple drugs in patients with bipolar disorder. Method: One hundred sixty-nine bipolar disorder outpatients diagnosed using the DSM-IV Structured Clinical Interview were included. Demographic and socioeconomic data, number of medications currently in use, history of suicide attempts, number of years undiagnosed, age of onset and current psychiatric co-morbidities were assessed using a structured questionnaire and DSM-IV criteria. The main outcome measure was the number of psychotropic drugs currently in use. Results: Approximately half of all patients (48.5%) presented a history of suicide attempt; 84% were using more than one medication, and 19% were using more than three drugs. The most frequent combinations of drugs used by these patients were: lithium + valproate (17%); lithium + antipsychotics (10%); lithium + valproate + antipsychotics (9%); and antidepressants + any drug (6%). The number of suicide attempts was associated with the use of multiple drugs. Conclusions: Our findings support the notion that the use of combination therapy in bipolar disorder may be related to severity of the BD, such as number of suicide attempts.

Descriptors: Bipolar disorder; Suicide; Polypharmacy; Suicide, attempt; Mood disorder

Resumo
Objetivo: O objetivo deste trabalho foi verificar associação entre tentativas de suicídio e uso de múltiplas drogas em pacientes com transtorno do humor bipolar. Método: Cento e sessenta e nove pacientes ambulatoriais com transtorno do humor bipolar, diagnosticados pela entrevista clínica estruturada do DSM-IV, foram incluídos. Dados demográficos e socioeconômicos, número de medicações em uso, história de tentativas de suicídio, número de anos sem diagnóstico, idade de início e comorbidades psiquiátricas foram avaliados através de um questionário estruturado e pelos critérios do DSM-IV. A principal medida de desfecho foi o número de medicamentos psicotrópicos usados correntemente. Resultados: Cerca de metade dos pacientes (48,5%) apresentou uma história de tentativas de suicídio; 84% estavam usando mais do que uma medicação e 19% estavam usando mais do que três medicações. As combinações de fármacos mais utilizadas por estes pacientes foram: lítio + valproato (17%); lítio + antipsicóticos (10%); lítio + valproato + antipsicóticos (9%); e antidepressivos + outros fármacos (6%). O número de tentativas de suicídio mostrou-se associado ao uso de polifarmácia, na análise ajustada. Conclusões: Nossos resultados sugerem que a polifarmácia em pacientes bipolares pode estar relacionada a indicadores de gravidade, como número de tentativas de suicídio.

Descritores: Transtorno bipolar; Suicídio; Polifármacos; Tentativa de suicídio; Transtornos do humor

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Introduction

Polypharmacy (PP) is the concurrent use of multiple drugs. In patients with multiple health problems; the use of PP has been associated with adverse drug reactions, drug interactions and an increased risk of hospitalization.[1-2]

The use of multiple drugs to treat bipolar disorder (BD) has increased in recent decades.[3] Such a rapid increase has not been accompanied by an equivalent increase in controlled trials assessing the efficacy and safety of drug combinations.[4] Evidence-based guidelines for the treatment of BD favor standard monotherapy regimens as the starting point of treatment.[5-7] However, patients who fail to respond to standard treatments tend to be exposed to multiple medications.[4]

There is a rationale for the use of drug combinations in BD patients.[8] Sensible medical reasoning for the use of multiple medications is possible up to a limit. In recent cohorts, more than 40% of BD patients were on three or more medications at hospital discharge.[3] It is difficult to retrieve the rationale used by clinicians at the time that patients were initiated on combination therapy. When it comes to using three or more drugs, other reasons apart from the evidence-based rationale seem to play an important role, since it has been recognized that there is a paucity of systematic studies in this area.[7] Recent research has shown that impulsiveness and severe anxiety, panic attacks, and agitation comorbid with depression are often immediate suicide risk factors that are potentially modifiable if recognized and treated urgently with effective medications and watchful support.[9]

In a previous study with 60 BD outpatients, we have shown that the time undiagnosed may play an important role in predicting clinical outcomes.[10] BD patients spent about 7.5 years from the time they received their first psychotropic prescription to the time that they were formally diagnosed as suffering from BD.[11] In the present study, 109 patients consecutively added to the sample previously described by Gazalle et al. were examined, in order to assess the association between number of suicide attempts and the use of multiple medications in BD patients.

Method

1. Study design

This study was a cross-sectional survey of 169 outpatients with BD, 18 years or older, consecutively assessed from September 2003 to February 2005.

2. Subjects

All patients were recruited from the Bipolar Disorders Program of the University Hospital of the Universidade Federal do Rio Grande do Sul, Porto Alegre (HCPA), Brazil. Porto Alegre has a population of 1.4 million inhabitants.[12] Patients were referred to the program by general practitioners and community based psychiatrists. Most patients are type-I BD, the remaining of the sample consisted of type-II BD and not otherwise specified BD, according to DSM-IV criteria.[13] About 80% of the patients had been already hospitalized due to an episode of BD. All patients were diagnosed and treated previously to the inclusion in the program.

3. Instruments and procedure

Qualified psychiatrists performed clinical interviews using the Structured Clinical Interview for DSM (SCID)[13-14] and a structured questionnaire. The variables of interest were number

Table 1 - Characteristics of the sample of bipolar disorder patients stratified by number of suicide attempts

Variable	Suicide attempts			
	0 (n = 87)	1-2 (n = 31)	>2 (n = 51)	P-value &
Sex				0.60*
Male	31.0%	22.6%	25.5%	
Female	69.0%	77.4%	74.5%	
Age (years)				0.99**
Mean (SD)	42.5 (12.8)	42.5(11.2)	42.3 (9.7)	
Age of first episode (years)				0.20**
Mean (SD)	26.7 (11.7)	24.8 (12.2)	23.0 11.9)	
Number of years undiagnosed				0.13**
Mean (SD)	9.1 (12.4)	13.0 (11.5)	12.7 (10.9)	
Current psychiatric morbidity				
Substance use disorders				
Alcohol abuse	2.5%	0.0%	1.5%	0.02*
Alcohol dependence	1.1%	0.0%	2.0%	0.06*
Substance abuse (other than alcohol)	1.1%	0.0%	8.0%	0.04*
Substance dependence (other than alcohol)	1.1%	0.0%	4.0%	0.05*
Psychosis	15.2%	19.4%	19.2%	0.23*
Somatoform disorder	2.5%	3.2%	1.9%	0.95*
Hypochondria	3.4%	9.7%	8.0%	0.59*
Body dysmorphic disorder	0.0%	6.5%	4.0%	0.09*
Bulimia nervosa	3.4%	3.2%	2.0%	0.88*
Anxiety disorders				
Social phobia	33.3%	29.0%	37.3%	0.04*
Specific phobia	32.2%	25.8%	38.0%	0.74*
Agoraphobia	12.6%	16.1%	24.0%	0.39*
Generalized anxiety disorder	8.0%	6.5%	16.0%	0.31*
Panic disorder	5.1%	16.1%	4.0%	0.57*
Obsessive compulsive disorder	5.7%	12.9%	14.0%	0.22*
Post-traumatic stress disorder	8.0%	9.7%	12.0%	0.17*

* Chi-square test   ** ANOVA & two degrees of freedom

of psychotropic drugs currently in use by each patient and the self-reported number of suicide attempts. Other variables evaluated were sex, age, family income, age of onset, number of years undiagnosed and current psychiatry co-morbidity.

4. Statistical analyses

Analyses were carried out using SPSS 10.0. Descriptive statistics included calculation of means and standard deviations for numeric variables, frequency and proportions for categorical ones. Patients were divided according to the number of suicide attempts (main exposure variable) into three groups (0, 1-2 or > 2). In order to test the association between number of suicide attempts and number of drugs used, Poisson regression models were used with number of psychotropic drugs currently in use as the outcome variable. First, an unadjusted regression was carried-out. Second, the association between number of medications currently in use and suicide attempts was adjusted for gender, age and family income. In the last model, extra adjustment was made by number of years undiagnosed, age of onset and current psychiatric morbidity. P-values were calculated using the Wald test for heterogeneity. All tests were two-tailed and the significance level used was 5%.

5. Ethical aspects

The Ethics Committee of the HCPA approved the study protocol (n. 03481) and the written informed consent was obtained from each participant after the procedures had been fully explained.

Results

Out of the 169 patients included, 85.7% were BD type I according to SCID classification; 26.9% had a rapid cycling presentation. Approximately half of all patients did not present a history of suicide attempt. Five in every six subjects (84%) were using more than one medication, and 19% were using more than three drugs. The most frequent
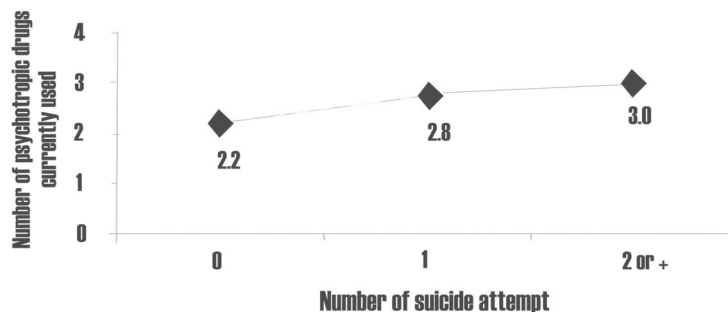

Figure 1 - Number of psychotropic drugs currently used according to the number of suicide attempts.
p = 0.001 (ANOVA test for trend)

combinations of drugs used by these patients were: lithium + valproate (17%); lithium + antipsychotics (10%); lithium + valproate + antipsychotics (9%); and antidepressants + any drug (6%).

Table 1 describes the patients in terms of demographic variables, age of onset, number of years undiagnosed and current psychiatric disorders stratified by number of suicide attempts. Patients who had social phobia (p = 0.04), alcohol (p = 0.02) and substance abuse (p = 0.04) or substance dependence (other than alcohol) (p = 0.05) had significantly higher number of suicide attempts. There was no statistically significant association between history of suicide attempts and sex, age, age of onset, number of years undiagnosed, alcohol dependence, psychosis, somatoform disorder, hypochondria, body dysmorphic disorder, bulimia nervosa and anxiety disorders except social phobia.

Figure 1 shows the crude association between the number of psychotropic drugs currently in use and the number of suicide attempts. There is a clear positive association between the variables. However, the crude association between the number of suicide attempts and the number of psychotropic

Table 2 - Crude and adjusted analysis of the association between number of suicide attempts and number of psychiatric drugs currently in use

Variable	Poisson regression coefficient	95% Confidence Interval	P-value
Number of suicide attempts			
0			
1	0.26	-0.02; 0.54	0.07
≥ 2	0.35	0.10; 0.59	< 0.01
Age	-0.01	-0.22; 0.11	0.43
Gender	-0.02	-0.26; 0.22	0.88
Family income	0.04	-0.22; 0.23	0.97
Number of years undiagnosed	0.00	-0.01; 0.02	0.68
Age of onset	0.10	-0.01; 0.03	0.21
Current psychiatry morbidity			
Alcohol abuse	0.76	-0.86; 2.38	0.36
Alcohol dependence	-0.05	-1.29; 1.19	0.94
Substance abuse	-0.14	-1.10; 0.82	0.78
Substance dependence	0.23	-0.94; 1.40	0.70
Psychosis	0.07	-0.19; 0.32	0.61
Somatoform disorder	0.15	-0.44; 0.75	0.61
Hypochondria	0.02	-0.51; 0.55	0.94
Body dysmorphic disorder	-0.26	-1.05; 0.52	0.52
Bulimia nervosa	0.31	-0.30; 0.91	0.32
Anxiety disorder			
Social phobia	0.01	-0.30; 0.33	0.99
Specific phobia	-0.07	-0.30; 0.16	0.56
Agoraphobia	-0.06	-0.37; 0.25	0.72
Generality anxiety disorder	0.16	-0.19; 0.51	0.38
Panic	-0.29	-10.5; 0.46	0.45
Obsessive compulsive disorder	0.15	-0.19; 0.50	0.38
Post-traumatic stress disorder	0.02	-0.40; 0.44	0.92

drugs currently in use might be an artifact due to confounding factors, including socio-demographic variables, number of years undiagnosed, age of onset, and current psychiatric co-morbidity. Therefore, it was important to test whether the association persists after adjusting for confounders.

Table 2 shows results of regression analysis. Adjustment for gender, age, family income, number of years undiagnosed, age of onset, and current psychiatric co-morbidity did not dilute the association between the number of suicide attempts and the number of psychotropic drugs currently in use. This means that the direct association between suicide attempts and use of multiple medications is independent of all possible confounding variables evaluated.

Discussion

The present study suggests that the number of suicide attempts is associated with the use of multiple drugs in BD. This association was unequivocal both in the unadjusted and adjusted analyses, suggesting that confounding was not responsible for our findings. The number of subjects included in the sample (n = 169) allowed a power greater than 80% to detect a mean difference of 0.40 medications. Because the actual difference was larger than 0.40, power was higher than expected. The reverse causality bias is frequent in cross-sectional studies such as ours. History of suicide attempts may increase the number of medication in use by patients, but the use of multiple drugs may also affect suicidality. Therefore, prospective studies are needed to confirm the direction of the association described here.

It is also important to consider that the number of suicide attempts was obtained directly from the patients, using a structured questionnaire. This may give rise to a recall bias, especially whenever the number of suicide attempts is concerned. The prevailing mood of the patients at the moment of the interview may also change the obtained information, since depressed patients are known to present a bias toward the retrieval of negative events. Another source of bias steams from the type of interpretation patients may give to their experiences. For instance, one patient many take an overdose and have it interpreted as a suicide attempt.

We acknowledge that other variables not included in this analysis, like personality factors, social support, stressors, and others may be also associated with suicide attempts, but it was impossible to consider all factors possibly associated with such a complex phenomenon like suicide attempts. However, this study considered a number of relevant variables, such as demographic and socioeconomic data, number of medications currently in use, number of years undiagnosed, age of onset, and current psychiatric co-morbidities. A possible limitation of our study is that we were not able to adjust for the therapeutic class of the medications used, due to sample size limitations. This would be important given the fact that the different medications used may be associated with the number of suicide attempts.

The cross-sectional nature of this study allows two main points to be developed:

1) Patients are likely to receive multiple drugs when pressing issues such as recurrent suicide attempts urge clinicians to take action. It is possible that the use of several medications reflects the fact that clinicians are likely to respond to severity of illness in a monotonic fashion, whereby the more severe is the case, the more medication the patient gets. There is evidence that patients who are submitted to multiple medications have an increased risk of side effects and early mortality,[15-16] meaning that the eagerness to cure by simply adding-on medication may do more harm than good.

2) It is important to highlight that the use of multiple medications does have some advantages. There is a rationale for the use of drug combinations in an array of cases of BD.[7] For instance, in acute mania, it has been shown that the use of antypsichotics in association with mood stabilizer may be more effective that mood stabilizers alone.[7] Because in our study the most frequent combinations of drug used include lithium, which is shown to be effective for preventing suicide,[17] these results may be interpreted as positive, and these patients may benefit from lithium in combination with other drugs.

Further studies, particularly prospective ones, are warranted in order to further clarify the association described in this paper.

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