Bipolar depression: the importance of being on remission

Depressão bipolar: a importância da remissão

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Abstract
Objective: The aim of the present study is to compare quality of life among currently depressed, subsyndromal and remitted patients with bipolar disorder (BD) and to assess whether the level of depression correlates with the scores of quality of life in BD patients. *Method*: Sixty bipolar outpatients diagnosed using the Structured Clinical Interview for DSM-IV who met criteria for diagnosis of BD type I, II or not otherwise specified (BD-NOS), and who were not currently on a manic or mixed episode were included. The main variables of interest were quality of life (QOL) assessed using the 26-item World Health Organization QOL instrument (WHOQOL-BREF) and depression assessed using the 17-item Hamilton Depression Rating Scale (HDRS). *Results*: A linear trend test showed a dose response association between patients' current mood state and all domains of quality of life. Higher quality of life scores were found among remitted patients, followed by subsyndromal patients; depressed patients presented lower scores of quality of life, except for the social domain. The four domains of the WHOQOL scale correlated negatively with the HDRS. *Conclusions*: Our findings suggest that bipolar depression and residual symptoms of depression are negatively correlated with QOL in BD patients.

Keywords: Subsyndromal; Bipolar disorder; Quality of life; Depression; Outpatients

Resumo
Objetivo: O objetivo deste estudo é o de comparar a qualidade de vida entre pacientes com transtorno bipolar que estão atualmente deprimidos, com depressão subsindrômica e com remissão de sintomas, e avaliar se o nível de depressão tem correlação com os escores de qualidade de vida em pacientes com transtorno bipolar. *Método*: Sessenta pacientes bipolares tratados ambulatorialmente, diagnosticados pela Entrevista Clínica Estruturada do DSM-IV, que preencheram critérios diagnósticos de transtorno bipolar tipo I, tipo II ou sem outra especificação (TB-SOE), e que não estavam atualmente em um episódio maníaco ou misto foram incluídos. As principais variáveis de interesse foram qualidade de vida, avaliada utilizando-se o instrumento de 26 questões de qualidade de vida da Organização Mundial de Saúde (WHOQOL-BREF) e depressão avaliada utilizando a Escala de 17 itens de Hamilton. *Resultados*: O teste de tendência linear mostrou uma associação dose-reposta entre o estado de humor atual do paciente e todos os domínios da qualidade de vida. Escores maiores de qualidade de vida foram encontrados entre pacientes com remissão completa dos sintomas, seguidos pelos pacientes com sintomas subsindrômicos. Os pacientes deprimidos apresentaram escores de qualidade de vida mais baixos que os demais, exceto no domínio social. Os quatro domínios da escala WHOQOL tiveram uma correlação negativa com a Escala de 17 itens de Hamilton para avaliação de depressão. *Conclusões*: Nossos achados sugerem que a depressão bipolar e os sintomas residuais de depressão estão negativamente correlacionados com qualidade de vida em pacientes com transtorno bipolar.

Descritores: Subsindrômico; Transtorno bipolar; Qualidade de vida; Depressão; Pacientes ambulatoriais

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Introduction

The rates of bipolar disorder (BD) in community samples are around 1%.[1] When less severe forms of the disorder are considered, the prevalence reported is around 6%.[2] Bipolar patients present major problems in dimensions related to quality of life, such as functional impairment, difficulties to sustain their jobs and interpersonal problems.[3] The World Health Organization estimates that BD is the fifth leading cause of disability among young adults.[4] The human and financial costs associated with this disorder are well established.[5] Given the size of the burden for patients and their families, BD is considered a major public health problem.[6]

Quality of life is an important variable which can be difficult to assess.[7] In recent years, several instruments have been put forward as a means to assess quality of life; most of these included different domains, such as physical, emotional, social and environmental. Quality of life instruments for specific patients are also available.[8-9] Functional impairment in patients with BD is probably related to residual symptoms, which can also predict episodic recurrence.[7] Quality of life seems to be impaired during mood episodes[10] but not in euthymic patients.[11] In patients with bipolar depression, quality of life was reported to be inversely correlated with the level of depression and to be worse in bipolar patients as compared to unipolar patients.[12]

The aim of the present study is to compare quality of life among currently depressed, subsyndromal and remitted patients with BD, and to assess whether the level of depression correlates with the scores of quality of life in bipolar patients.

Method

1. Study design

This study was a cross-sectional survey of 60 outpatients with BD, 18 years or older, consecutively assessed from September 2003 to August 2004. Patients were grouped according to their depressive symptoms into three categories, namely: 1) Depressed: patients who met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)[13] criteria for current major depressive episode; 2) Subsyndromal: patients who did not meet DSM-IV criteria for current major depressive episode, but presented a 17-item Hamilton Depression Rating Scale (HDRS)[14] score > 7; 3) Remitted: patients who did not meet DSM-IV criteria for current major depressive episode and presented a HDRS < or = 7.[15]

2. Setting

All patients were recruited from the Bipolar Disorders Program of the University Hospital at the Federal University, Porto Alegre, Brazil. Porto Alegre is a southern Brazilian city with a population of 1.4 million inhabitants; health-related variables tend to be better in Porto Alegre in comparison to Brazil as a whole. For example, while infant mortality for the whole country was reported to be of 28.3 per 1,000 live births, this rate was 14.3 in Porto Alegre.[16]

3. Patient selection

Patients who met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)[13] criteria for BD type I, II and not otherwise specified (NOS) were included. Patients who were in currently manic or in a mixed episode were excluded.

4. Assessment

Patients were interviewed by trained psychiatrists using the Structured Clinical Interview for DSM-IV (SCID).[17] The primary variables of interest were quality of life and depression. Quality of life was assessed using the 26-item World Heath Organization quality of life instrument (WHOQOL-BREF)[18] and depression was assessed using the 17-item Hamilton Depression Rating Scale (HDRS).[14] Demographic data were collected using a structured and pre-tested questionnaire.

5. Statistical analyses

The HDRS scale was treated as a categorical variable (≤ 7 vs. > 7), to define remitted and subsyndromal patients. The four domains of WHOQOL's quality of life (physical, psychological, social and environmental) were analyzed separately.

Table 1 - Demographics of the sample

Variable	Bipolar patients' current mood status			p value
	Depressed	Subsyndromal	Remitted	
	(n = 27)	(n = 14)	(n = 19)	
Sex				
Men	18.5%	28.6%	31.6%	0.31*
Women	81.5%	71.4%	68.4%	
Age (years)				
Mean (SD)	40.2 (11.2)	36.0 (10.1)	41.8 (9.0)	0.72**
< 40	40.7%	48.5%	42.0%	0.21*
40-59	59.3%	42.4%	58.0%	
≥ 60	0.0%	9.1%	0.0%	
Family income (US$)				
Median	91	100	96	0.50***
1st tercile	32.0%	40.6%	38.5%	0.80*
2nd tercile	32.0%	28.1%	41.2%	
3rd tercile	36.0%	31.3%	20.3%	
Schooling (years)				
Mean (SD)	9.6 (3.1)	9.0 (4.6)	9.4 (3.2)	0.91**
0-8	33.3%	32.1%	36.5%	0.81*
9-11	44.5%	38.6%	32.5%	
≥ 12	22.2%	29.3%	31.0%	

* Chi-square test; ** T-test; *** Kruskal Wallis test
Depressed: patients who met DSM-IV criteria for current bipolar depression episode
Subsyndromal: patients who did not meet DSM-IV criteria for current bipolar depression episode and presented a 17-item Hamilton Depression Rating Scale (HDRS) > 7
Remitted: HDRS < or = 7

Descriptive analyses included calculation of proportions and respective 95% confidence intervals for categorical variables, and means, medians, standard deviations and percentiles for continuous variables. Histograms and the Kolmogorov-Smirnov test were used to check variables for normality. Pearson correlation coefficients were used to examine the relationship between continuous variables. The chi-square tests for heterogeneity and for linear trend were used in order to test differences in proportions. The non-parametrical Kruskal-Wallis test was applied to compare medians, while t-test and analysis of variance (for heterogeneity and for linear trend) were employed to compare means.

The Ethics Committee of the HCPA approved the study protocol (n: 03481), and each patient gave written informed consent prior to the interview.

Results

Table 1 describes patients in terms of demographic characteristics. No significant differences were observed among groups.

The mean values and standard deviations of the four domains of the WHOQOL for the whole sample were: physical (mean: 50.1 SD 19.0), psychological (mean 52.5 SD 20.2), social (mean 53.9 SD 15.3) and environmental (mean 51.2 SD 21.4). These four continuous variables presented normal distributions, as confirmed, graphically and by the Kolmogorov-Smirnov test. In terms of Hamilton depression rating scale (HDRS), the mean value was 9.7 (SD 6.5).

The four domains of the WHOQOL scale correlated negatively with the HDRS, as well as with Pearson correlation coefficients, ranging from -0.33 (environmental domain) to -0.56 (psychological). All p values were statistically significant (Figure 1). Table 2 shows the mean values of each WHOQOL domain according to the patients' current mood state as it was

classified in Table 1. Linear trend tests confirmed a dose response association between patients' current mood state and all domains of quality of life, although the p value for the physical domain had a borderline significance (p = 0.08). Higher quality of life scores were found among remitted patients, followed by subsyndromal patients; depressed patients presented lower scores of quality of life, except for the social domain.

Discussion

The present study showed that depressive symptoms are determinant of quality of life in patients with BD. Even more important than this, our data indicate that among patients who are not currently in a depressive episode, that is those presenting subsyndromal symptoms of depression, have a worse quality of life than patients on remission. These results occurred across all domains of quality of life, with the greatest effect size in the psychological domain, and the lowest one in the physical domain.

One should bear in mind that a sample of 60 patients is rather too small to allow a wider generalization of these findings. However, lack of power was not a problem in our analyses, given the size of the differences between depressed patients and the remaining sample. Actually, the statistical power was above 80% for most analyses presented in this paper. Therefore, a bigger sample size would probably leave our results unchanged.

A community-based control group would be necessary to compare BD patients with the general population.[19-20] Nevertheless, this was not this investigation goal. For the purposes of the present study, the use of an internal control group decreased the likelihood of confounding effects, thereby reinforcing our findings.

Previous studies of quality of life in BD patients[11,21] did not account for the importance of subsyndromal symptoms of
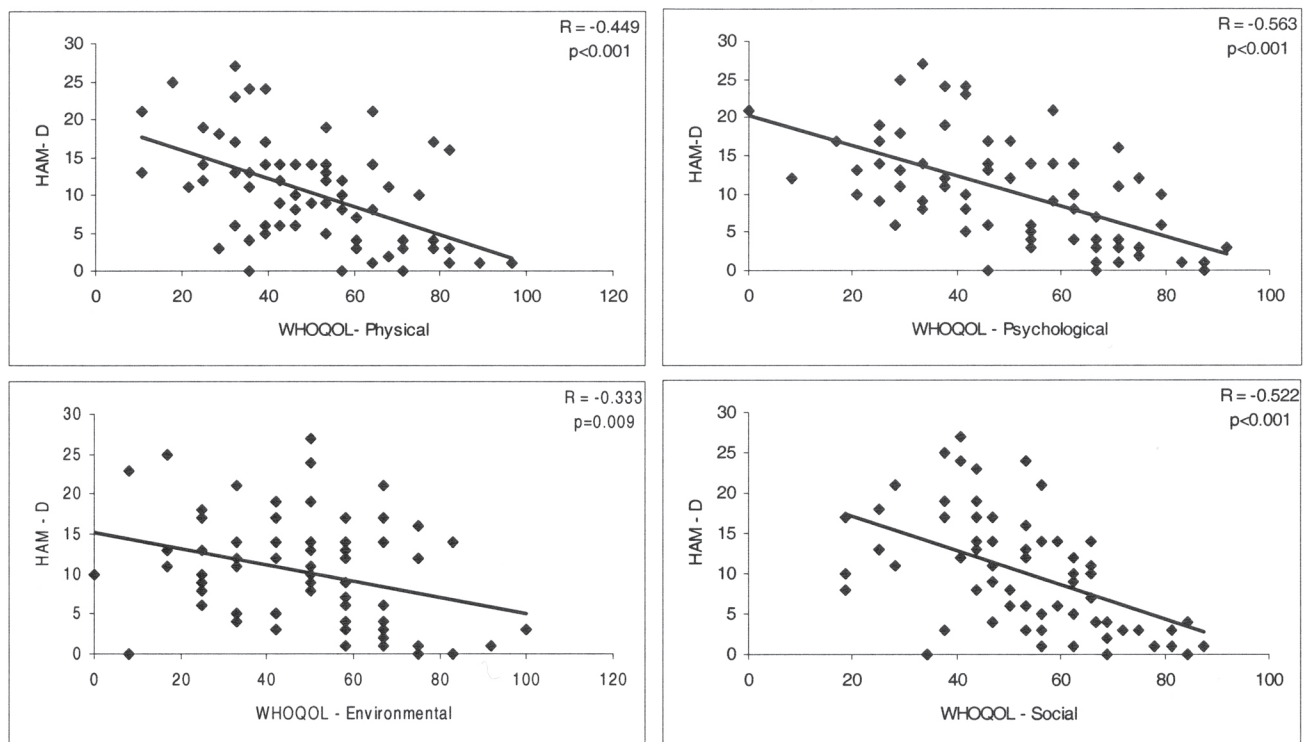

Figure 1 - Relation between quality of life domains and Hamilton Depression Rating Scale

Table 2 - Domains of quality of life in patients with bipolar disorder

Domains of Quality of Life (WHOQOL)	Bipolar patients' current mood status			p value
	Depressed	**Subsyndromal**	**Remitted**	
	(n = 27)	(n = 14)	(n = 19)	
Physical	48.3 (19.9)	50.7 (18.1)	58.5 (17.3)	0.19* 0.08**
Psychological	45.1 (19.2)	50.3 (20.0)	64.9 (16.5)	0.003* 0.001**
Social	50.2 (13.1)	46.9 (16.0)	64.4 (13.0)	0.001* 0.002*
Environmental	46.0 (14.7)	48.8 (24.2)	60.5 (25.1)	0.07* 0.03**

ANOVA test for heterogeneity
*** ANOVA test for linear trend*
WHOQOL: 26-item World Health Organization quality of life instrument (WHOQOL-BREF)
Depressed: patients who met DSM-IV criteria for current bipolar depression episode
Subsyndromal: patients who did not meet DSM-IV criteria for current bipolar depression episode and presented a 17-item Hamilton Depression Rating Scale (HDRS) > 7
Remitted: HDRS < or = 7

depression, which is desirable for a better understanding of the effects of psychiatric treatment on quality of life.[22] Our results suggest that treating subsyndromal symptoms of depression may be an important factor for the improvement of quality of life among BD patients.

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References

1. Merikangas KR, Chakravarti A, Moldin SO, Araj H, Blangero, JC, Burmeister M, Crabbe J Jr, Depaulo JR Jr, Foulks E, Freimer NB, Koretz DS, Lichtenstein W, Mignot E, Reiss AL, Risch NJ, Takahashi JS. Future of genetics of mood disorders research. *Biol Psychiatry*. 2002;15;52(6):457-77.
2. Judd LL, Akiskal HS. The prevalence and disability of bipolar spectrum disorders in the US population: re-analysis of the ECA database taking into account sub threshold cases. *J Affect Disord*. 2003;73(1-2):123-31.
3. Dean BB, Gerner D, Gerner RH. A systematic review evaluating health-related quality of life, work impairment, and healthcare costs and utilization in bipolar disorder. *Curr Med Res Opin*. 2004;20(2):139-54.
4. Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: global burden of disease study. *Lancet*. 1997;349(9063):1436-42.
5. Dunner DL. Clinical consequences of under-recognized bipolar spectrum disorder. *Bipolar Disord*. 2003;5(6):456-63.
6. Belmaker RH. Bipolar disorder. *N Engl J Med.* 2004;351(5):476-86.
7. MacQueen GM, Marriott M, Begin H, Robb J, Joffe RT, Young LT. Subsyndromal symptoms assessed in longitudinal, prospective follow-up of a cohort of patients with bipolar disorder. *Bipolar Disord*. 2003;5(5):349-55.
8. Badia X, Webb SM, Prieto L, Lara N. Acromegaly Quality of Life Questionnaire (AcroQoL). *Health Qual Life Outcomes*. 2004;2(1):13.
9. Moy ML, Israel E, Weiss ST, Juniper EF, Dube L, Drazen JM. NHBLI Asthma Clinical Research Network. Clinical predictors of health-related quality of life depend on asthma severity. *Am J Respir Crit Care Med*. 2001;163(4):924-9.
10. Namjoshi MA, Buesching DP. A review of the health-related quality of life literature in bipolar disorder. *Qual Life Res*. 2001;10(2):105-15.
11. Chand PK, Mattoo SK, Sharan P. Quality of life and its correlates in patients with bipolar disorder stabilized on lithium prophylaxis. *Psychiatry Clin Neurosci*. 2004;58(3):311-8.
12. Yatham LN, Lecrubier Y, Fieve RR, Davis KH, Harris SD, Krishnan AA. Quality of life in patients with bipolar I depression: data from 920 patients. *Bipolar Disord*. 2004;6(5):379-85.
13. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington, DC: American Psychiatric Press; 2000.
14. Moreno RA, Moreno DH. Escalas de Avaliação para Depressão de Hamilton e Montgomery-Asberg. In: Gorenstein C, Andrade LHSG, Zuardi AW, eds. Escalas de Avaliação Clínica em Psiquiatria e Psicofarmacologia. São Paulo: Lemos Editorial; 2000. p. 71-87.
15. Zimmerman M, Chelmiski I, Posternak M. A review of studies of the Hamilton depression rating scale in healthy controls: implications for the definition of remission in treatment studies of depression. *J Nerv Ment Dis*. 2004;192(9):595-601.
16. Instituto Brasileiro de Geografia e Estatística. Síntese de Indicadores Sociais. 2000. [citado 15 dez]. Disponível em: http://www.ibge.com.br.
17. First MB, Spitzer RL, Gibbon M, Williams JB. User's guide to the structured clinical interview for DSM-IV (SCID-I). New York: Biometrics Research; 1996.
18. Fleck MP, Louzada S, Xavier M, Chachamovich E, Vieira G, Santos L, Pinzon V. Aplicação da versão em português do instrumento abreviado de avaliação da qualidade de vida "WHOQOL-bref". *Rev Saude Publica*. 2000;34(2):178-83.
19. Robb JC, Cooke RG, Devins GM, Young LT, Joffe RT. Quality of life and lifestyle disruption in euthymic bipolar disorder. *J Psychiatr Res*. 1997;31(5):509-17.
20. Arnold LM, Witzeman KA, Swank ML, McElroy SL, Keck PE Jr. Health-related quality of life using the SF-36 in patients with bipolar disorder compared with patients with chronic back pain and the general population. *J Affect Disord*. 2000;57(1-3):235-9.
21. Kusznir A, Cooke RG, Young LT. The correlates of community functioning in patients with bipolar disorder. *J Affect Disord*. 2000;61(1-2):81-5.
22. Rasgon N, Bauer M, Grof P, Gyulai L, Elman S, Glenn T, Whybrow PC. Sex-specific self-reported mood changes by patients with bipolar disorder. *J Psychiatr Res*. 2005;39(1):77-83.