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ORIGINAL ARTICLE

Subsyndromal anxiety: Does it affect the quality of life? A study on euthymic patients with bipolar disorder

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Abstract
Background and objectives: Patients with bipolar disorder (BD) have a severely impaired quality of life (QoL), even when euthymic. The impact of subsyndromal affective symptoms and comorbid anxiety disorders has been clearly established. However, once an anxious comorbid disorder has been ruled out, no attention is paid to current anxiety. The aim was to determine whether subsyndromal anxiety impacts on current QoL in euthymic BD patients, regardless of comorbid anxiety disorders.
Methods: Euthymic BD patients attending the National Institute of Psychiatry were assessed for perceived QoL and current anxiety symptoms. Presence or absence of comorbid anxiety disorders was established by the treating psychiatrist.
Results: 60 patients, (86.7% with type I BD) with a mean age of 47.2 years (SD = 11) were included. Mild to moderate symptoms of anxiety were reported and 20% of the patients had a Poor-QoL. Patients with Poor-QoL exhibited higher subsyndromal manic symptoms (Cohen $d = 0.83$) and higher anxiety symptoms (Cohen $d = 1.04$). Anxiety symptoms were the most important predictor for Poor-QoL in BD patients (OR = 1.05).
Conclusion: The presence of anxious symptoms, even in patients without a comorbid anxious disorder, impact QoL negatively in euthymic BD patients. Their assessment and effective treatment should be included in routine clinical practice.

Introduction

In the past, the main outcome in clinical trials on bipolar disorder was the reduction of symptoms of mania or depression, rather than the recovery of social functioning. The focus of

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research and practice in bipolar disorder (BD) is shifting, with greater attention being paid to people's experience of living with the condition.[1] Indeed, although BD's prevalence is lower in comparison to major depressive disorder and anxiety disorders, it's severe impairment in functioning and quality of life (QoL) result in a greater economic burden for society.[2]

Comorbid psychiatric disorders certainly play a role on the QoL, and anxiety disorders are among the most prevalent comorbid disorders in BD, with an estimated lifetime prevalence of any anxiety disorder at over 40% in several studies.[3–6] The impact on the Current and lifetime prevalence of comorbid anxiety disorders, have been associated with intensified symptoms of bipolar disorder and additional comorbid disorders, resulting in a negative impact on the patient, on the course of the illness, greater disability and a lower quality of life, even in euthymic patients.[7–11] The presence of anxiety in bipolar patients is also associated with a lowered age at onset,[12] hampered patient response to treatment such as lithium,[13] higher overall BD illness severity, depressive severity, manic episode severity,[13,14] and increased rates of suicide and substance abuse.[3]

However, once comorbidity with anxiety disorders has been ruled-out, no attention is paid to the impact of subsyndromal anxiety (defined as symptoms of anxiety that do not fulfill criteria for an anxiety disorder) as can be observed by the lack of scales aimed at measuring anxiety on studies on QoL in BD.[15]

However, in clinical practice, anxious symptoms become evident on the evaluation of the patient with BD, especially once you start looking for them. As Karpov and colleagues described, ''comorbid anxiety symptoms are ubiquitous among psychiatric patients with mood or schizophrenia spectrum disorders''.[16] Indeed, anxiety and mood disorders tend to co-exist.[17] Furthermore, even subthreshold anxiety affects functioning as an isolated condition.[18] Therefore, the aim of the present study was to determine whether anxious symptoms impact current QoL in euthymic BD patients, regardless of comorbid generalized anxiety disorder.

Material and methods

This study was approved by the Ethics and Scientific Committees of the *Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz* (INPRF). After having received an explanation on the nature of the study, participants gave their written consent to participate.

Participants

Patients with bipolar disorder according to DSM-5 criteria[19] were recruited from October 2015 to December 2017 from the Affective Disorders' Clinic of the National Institute of Psychiatry in Mexico City. The diagnosis of BD had to be stable for at least the past two years; participants had to have been evaluated in at least one occasion by a specialist in BD from the Clinic, asserting the diagnosis. Patients were included if: (a) they had been euthymic for at least two months according to medical records, (b) had not been hospitalizned in the prior 6 months, and (c) had not had suicide attempts in the prior 6 months. Euthymia was further confirmed by having a score <8 on the Young Mania Rating Scale (YMRS) and a score <9 on the Hamilton Depression Rating Scale (HDRS) on the day of evaluation.[20] Patients were not included if they had active alcohol and/or substance abuse or dependence, comorbid axis I disorders (except Generalized Anxiety Disorder (GAD) or Panic Disorder (PD)) or neurological illness according to medical records. Psychiatric comorbidities were recorded from medical records. In total, 92 patients were invited, 4 refused to participate, 24 did not meet inclusion criteria and 4 did not complete all questionnaires; from de remaining 60, 27(45%) had comorbid GAD. PD was not found in our sample.

Obtention of retrospective clinical variables

Clinical variables such as age at onset, years of illness evolution, number of episodes, number of hospitalizations and polarity of episodes were obtained from clinical records to avoid memory bias.[21] A document with strict definitions to record variables was drafted and inter-rater reliability was assessed using Cohen's Kappa in a sample of 10 clinical records obtaining substancial agreement with Kappa values > 0.75 in the included variables (Appendix 1).

Assessment procedure

Anxiety was evaluated with the Inventory of Anxiety Situations and Answers, brief version (ISRA-B). The Inventory of Anxiety Situations and Answers was developed in 1984 by Miguel-Tobar and Cano-Vindel to evaluate general anxiety. It is formed by 3 anxious responses subscales (cognitive, physiologic and motor) and 4 subscales of stressful situations (evaluation, interpersonal, phobic and ordinary).[22] Its brief version, ISRA-B, comprises 46 items scored from 0 (hardly ever) to 4 (almost always), obtaining 3 scores: general anxiety score, situational areas score and global score. For the present study, we only considered the general anxiety score, which can range from 0 to 96, with higher scores as indicative of more severe anxiety symptoms. This version has been adapted for Mexican population where a percentile 50 corresponds to a general anxiety score of 21 in women and 17 in men; percentile 75 corresponds to a general anxiety score of 30 in women and 26 in men.[23]

Quality of life was measured using the Quality of Life in Bipolar Disorder (QoL.BD) scale, an instrument developed specifically for BD by Michalak and Colleagues (2010). It comprises 56 items rated from 1 to 5, evaluating the following domains: physical, sleep, mood, cognition, leisure, social, spirituality, finances, household, self-esteem, independence, identity, work, education. A global score is obtained with higher scores indicating a better quality of life. The proposed cut-off point of 170 has shown adequate sensitivity and specificity values (>0.80).[24] With this score, our sample was divided into two groups: Poor-QoL and Adequate-QoL. Poor-QoL was defined as having a total QoL.BD score under 170 for participants who neither worked nor studied, under 174 for participants who either worked or studied and under 178 for participants who both worked and studied. This scale has been adapted to Latin population.[25]

Table 1 Demographic and clinical characteristics according to QoL status.

	Total sample $n=60$		Adequate QoL $n=48$		Poor QoL $n=12$		Statistic
***n* %**							
Gender – Women	45	75.0	34	70.8	11	91.7	$\chi^2=2.2$, $p=0.13$
Low Socioeconomic status	40	66.7	31	64.6	9	75.0	$\chi^2=0.4$, $p=0.49$
Remunerated activity	37	61.7	32	66.7	5	41.7	$\chi^2=2.5$, $p=0.11$
Diagnoses – BD I	52	86.7	42	87.5	10	83.3	$\chi^2=0.1$, $p=0.70$
Previous psychiatric hospitalization	50	83.3	40	83.3	10	83.3	-
Comorbid GAD-present							
Treatment – current	27	45.0	21	43.8	6	50.0	$\chi^2=0.1$, $p=0.69$
Lithium	28	46.7	22	45.8	6	50.0	$\chi^2=0.06$, $p=0.79$
Anticonvulsive	41	68.3	33	68.8	8	66.7	$\chi^2=0.01$, $p=0.89$
Antipsychotic	37	61.7	27	56.3	10	83.3	$\chi^2=2.9$, $p=0.08$
Antidepressant	14	23.3	12	25.0	2	16.7	$\chi^2=0.3$, $p=0.54$
Benzodiazepines	25	41.7	19	39.6	6	50.0	$\chi^2=0.4$, $p=0.51$
Mean S.D.							
Current age	47.2	11.0	48.1	10.9	43.8	11.2	$t=1.2$, $p=0.23$
Years of education	13.7	3.7	13.7	3.8	13.5	3.2	$t=0.2$, $p=0.83$
Age of illness onset	25.0	8.7	25.4	9.2	23.0	6.4	$t=0.8$, $p=0.40$
Illness evolution (years)	22.9	9.5	23.0	9.4	22.3	10.5	$t=0.2$, $p=0.82$
Number of psychiatric hospitalizations	2.3	1.8	2.3	1.9	2.0	1.4	$t=0.6$, $p=0.54$
Clinical episodes (number)	10.5	5.5	10.7	5.6	9.5	5.2	$t=0.6$, $p=0.50$
Depressive episodes	5.7	4.2	5.7	4.2	5.8	4.5	$t=-0.07$, $p=0.94$
Manic episodes	3.5	2.5	3.6	2.6	2.7	1.9	$t=1.1$, $p=0.24$
HDRS score	2.3	2.4	2.1	2.2	3.2	3.0	$t=-1.4$, $p=0.15$
YMRS score	1.2	1.6	0.9	1.5	2.2	1.6	$t=-2.6$, $p=0.01$ Cohen $d=0.83$
ISRA-B score	24.2	17.9	20.4	15.1	39.5	20.9	$t=-3.6$, $p=0.001$ Cohen $d=1.04$

Statistical analysis

Descriptive statistics of all variables were calculated. Demographic and clinical variables were tested for differences between QoL groups with χ^2 or with independent sample t tests. Effect size (Cohen *d*) was computed for the significant results from the comparative analyses. Effect sizes were interpreted as small ($d=0.2$), medium ($d=0.5$), and large ($d=0.8$).[26] All variables with significant differences in the comparative analyses were included in multivariate logistic regression analyses as explanatory variables and Poor-QoL as the outcome variable. Significance level for tests was set at the 0.05 level. All statistical procedures were performed using the *Statistical Package for the Social Sciences* (SPSS), version 21.

Results

A total of 60 BD patients completed the clinical assessment. Most patients were women (75.0%, $n=45$). The mean age of the sample was 47.2 years (S.D. = 11.0, range 19–71) with a mean education of 13.7 years (S.D. = 3.7, range 3–20). More than half (66.7%, $n=40$) reported to have a low socio-economic status and 61.7% ($n=37$) had a remunerated activity.

Most of the patients were diagnosed with BD I (86.7%, $n=52$). Mean age at illness onset was 25.0 years (S.D. = 8.7, range 5–45), with an illness evolution of 22.9 years (S.D. = 9.5, range 6–57). The mean number of mood episodes was 10.5 episodes (S.D. = 5.5, range 2–27) with more depressive episodes (mean 5.7, S.D. = 4.2, range 0–19) than manic ones (mean 3.5, S.D. = 2.5, range 0–12). Fifty patients (83.3%) had a history of psychiatric hospitalization with a mean of 2 hospitalizations (S.D. = 1.8, range 1–7) (S.D. = 1.0, 1–5 hospitalizations). Twenty-seven patients (45.0%) had an additional diagnosis of generalized anxiety disorder (GAD). At the time of the study, all patients were under pharmacological treatment and euthymic according to medical records and the mean scores of the HDRS and YMRS scales shown in Table 1. The most frequently reported symptoms of mania were irritability (21.6%, $n=13$), decrease need for sleep (13.3%, $n=8$), increased rate in speech (11.6%, $n=7$), appearance (10.0%, $n=6$), thought disorder (6.6%, $n=4$) with a maximum item-score of mild severity. The mean score of the ISRA-B anxiety scale was 24.2 (S.D. = 17.9, range 0–76). Patients with GAD reported similar ISRA-B scores ($n=27$, mean score=28.6, S.D. = 19.3) than patients without comorbid GAD ($n=33$, mean score = 20.7, S.D. = 16.2; $t=-1.7$, $p=0.09$). According to the proposed cut-off point of the QoL.BD scale, 20.0% ($n=12$) of the patients had a Poor-QoL. Demographic and clinical characteristics by current QoL status are shown in Table 1.

Table 2 Logistic regression model for Poor-QoL in study participants.

	β	*Odds ratio*	*95% C.I.*	*p*
Manic symptoms (YMRS score)	0.33	1.40	0.94–2.08	0.09
Anxiety symptoms (ISRA-B score)	0.05	1.05	1.01–1.10	0.01

As can be seen, no differences emerged between QoL groups in terms of demographic features or clinical characteristics related to the course of BD, such as years of evolution or number of episodes. However, patients with Poor-QoL exhibited higher manic and anxiety symptoms according to the YMRS and ISRA-B scales respectively, both comparisons with large size effects (Cohen $d > 0.8$).

A logistic regression analysis was conducted to examine predictors of Poor-QoL among the study population. The YMRA and ISRA-B scores were entered in the model. As displayed in Table 2 the only significant predictor for Poor-QoL in BD patients in the presence of current symptoms of anxiety.

Discussion

The aim of the present study was to determine whether anxious symptoms and clinical features of BD impact current QoL in euthymic BD patients, regardless comorbid generalized anxiety disorder. The present study adds evidence of the importance of recognizing anxious symptoms in BD patients, even without a categorical diagnosis of an anxiety disorder and after achieving euthymia. Anxious symptoms, which were quite remarkable in the studied sample, affected perceived quality of life more than subthreshold symptoms of mania and depression and more than other variables related to the evolution of BD, such as number of hospitalizations and even the comorbid diagnosis of GAD. The results found in the large effect size and inclusion in the logistic regression of subthreshold manic symptoms, may reflect a probable Type II error. However, we consider that this might also be representing the presence of anxious symptoms as the most frequent item of the YMRS with a score above 0 (found in 13 patients from our sample) was item number 5: irritability, which can also be present in anxiety.[27]

In general, what is expected for recovery in BD patients is the remission of manic or depressive symptoms, that is, that patients reach euthymia. However, as can be seen in our results, there are other symptoms that may impede patients' well-being and even their full recovery and reintegration to a productive life[28] and that should always be considered during their attendance to a mental health service. Anxious symptoms may be one of these major barriers on the road to recovery for BD patients. The impact of anxiety disorders in the clinical course and treatment response of this disorder has been previously described[29] and the comorbidity, particularly with generalized anxiety disorder and panic disorder, is common.[6,30] The present manuscript showed that other important areas such as quality of life are also affected by anxiety even without having an established diagnosis of an anxiety disorder. Current pharmacological treatments for BD are not effective for the treatment of anxious symptomatology[31] and first line treatments for anxiety disorders negatively impact the course of BD, especially in type I BD.[32] Therefore, a case-by-case analysis has to be implemented when anxiety is present in a patient with BD, considering non-pharmacological options, such as psychotherapy.[33]

While our results highlight the importance of the assessment of anxiety in BD patients, it is noteworthy to consider the cross-sectional nature of our study and that anxious symptom severity as well as the perceived QoL may be affected by other variables not assessed in the present study such as neurocognition, physical health, personality features and sociocultural surrounding, variables that should be further assessed in future studies to determine which other factors are related to a low quality of life in BP. With this, it would be possible to develop health-interventions aimed at its improvement.

Another important limitation in our study is that psychiatric comorbidities were not confirmed using a semi-structured clinical interview, especially for anxious disorders. The scores in the ISRA-B anxiety scale found in our patients suggest that clinicians might be underlooking anxiety in this population even though clinical assessment of the patients follows current DSM criteria. We hypothesize that evaluation of anxious disorders may not be performed systematically, in clear contrast to the assessment of depressive or manic symptoms, as core features of bipolar disorder. Nevertheless, our findings show that whether a categorical diagnosis exists or not, anxious symptoms affect the quality of life of our patients and should therefore be routinely evaluated for their presence and severity.

The present study showed how the core symptoms related to BD are not the only features that negatively impact the course and prognosis, as other symptoms, not typically associated with the diagnosis, may be present. Mental health professionals should bear in mind that the diagnostic criteria used until now to classify mental disorders are useful to give a standardized definition of the disorder but are not sufficient to give a broad vision of the disorder in each patient. Classic descriptions of manic-depressive illness which highlighted the presence of anxious symptoms should not be forgotten, and neither should the anxious symptom specifier.

Conclusions

Our results emphasize the need to perform a clinical assessment that includes other non-primary diagnostic symptoms in BP that may be currently affecting the patient. In this way, these symptoms can be treated in an effort to enhance BD patients' quality of life, clinical and functional recovery.

Given the past and current evidence of the role played by anxiety in BD, it is warranted to ask: are patients really

euthymic when anxiety is still present? Is anxiety a comorbid condition or should we consider it a core feature of BD?

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Conflict of interest

The authors have no conflict of interest to declare.

Appendix 1. Obtention of retrospective clinical variables

Clinical variable	Cronbach's alpha
Age at onset	0.962
Number of episodes	0.826
Number of hospitalizations	0.972
Number of suicide attempts	0.889
Comorbidity with Generalized Anxiety Disorder	0.753

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