Brief report

Subsyndromal depressive symptoms in patients with bipolar and unipolar disorder during clinical remission

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Abstract

Background: Subsyndromal depressive symptoms seem to be quite prevalent in mood disorders although very few studies have assessed them in patients considered to be in remission by clinical and psychometric criteria. This study sought to evaluate the presence of subsyndromal depressive symptoms in bipolar and unipolar patients in clinical remission.

Methods: One-hundred seventy-six patients with DSM-IV bipolar (62 bipolar I, 58 bipolar II) or unipolar major depression (n = 58) in clinical remission and 60 healthy subjects were assessed using several psychometric instruments including the 17 items Hamilton Depression Rating Scale (HDRS). To be considered in clinical remission patients assessed with the Clinical Impression for Bipolar Disorder-Modified (CGI-BP-M) had to be stable for 6 months and scoring 6 or less in the Young Mania Rating Scale (YMRS) and 8 or less in the HDRS.

Results: Both Unipolar Disorder (UD) and Bipolar Disorder (BD) patients in clinical remission presented statistically significant higher HRSD scores, than healthy subjects. The HRSD scores were statistically higher in UD patients under remission than in BD patients.

Conclusion: Subsyndromal depressive symptoms are present in affective disorder patients, both UD and BD, who apparently are in clinical remission. Remitted unipolar patients may have more residual symptoms than bipolar patients, particularly in items related to anxiety and somatic complaints.

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1. Introduction

A large number of patients who have suffered acute mood disorder episodes continue presenting subsyndromal symptoms during remission periods of apparent clinical stability (Benazzi, 2002). Several studies have
focused on the comorbidity pattern in patients with bipolar disorder (BD) during remission periods; among BD type I patients, comorbidity with other psychiatric conditions has been reported in 31% of patients of the studied samples (Vieta et al., 2001a, 2001b); this comorbidity having a definite relevance in the course and outcome of bipolar disorder patients. Comorbidity studies on BD type II patients, showed a prevalence of axis I disorders of 35%; suicidal ideation and suicide attempts are more frequent in patients exhibiting this comorbidity (Vieta et al., 2000).

More specifically, in prospective studies in BD patient samples, comorbid symptoms have been described during remission, these being predominantly depressive in about a 45% of the patients (Post et al., 2003; Judd et al., 2003, 2002); BD type I patients can spend a third of the year suffering from depression when they are evaluated with Life Chart Method techniques combined with regular clinical interviews during follow-up. In a recent study involving 759 adult outpatients, subsyndromal depressive symptoms were associated with functional impairment in several life domains i.e. work, home functioning roles and relations with family and friends (Altshuler et al., 2006). More generally, it has been suggested that BD outpatients during remission show specific clinical features (Perlis et al., 2006).

These data seem to suggest an association between depression, suicidality and comorbidity in BD. Thus, an accurate description and a better definition of disease-specific symptoms during remission, could help to improve detection of BD patients presenting with a variety of complaints in everyday psychiatric practice.

Moreover, it has been described that subsyndromal symptoms upon remission have a strong prognostic value in mood disorders in general (Fava, 1999), and may predict relapse into syndromal depression specifically in BD (Altshuler et al., 2006).

Baseline data from the hypomania detection study (EDHIPO) (Vieta et al., 2006) to validate into Spanish BD screening instruments, provide the opportunity to gain a clinically useful insight of the presence and nature of subsyndromal depressive symptoms in psychiatric patients with mood disorders and healthy controls.

The following questions were posed for this post-hoc analysis: 1) How strong is the association between subsyndromal depressive symptoms and particular mood disorders including BD and major depression (MD) diagnosed patients? 2) Are there special features of subclinical symptoms during clinical remission that would improve detection of BD patients at this stage? 3) Is there a relationship between subsyndromal symptoms and the course duration of BD? These questions were addressed by comparing baseline clinical results between three mood disorder patients’ groups (BDI, BDII and MDD) and healthy controls.

2. Methods

In order to assess subsyndromal depressive symptoms in apparently euthymic DSM-IV depressed bipolar I, II and unipolar patients, 60 healthy control subjects (CS), 62 bipolar I(BDI), 56 bipolar II(BDII) and 58 unipolar patients(UD) in remission were enrolled in the EDHIPO study (Table 1). The baseline cross-sectional of this study results are being used for this analysis.

To determine the stability of the disease in the first study visit, we assessed all the participants using the Young Mania Rating Scale (YMRS) (Colom et al., 2002), the 17-item Hamilton Depression Rating Scale (HDRS-17) (Bobes et al., 2003), and the Modified Clinical Global Impression Scale for Bipolar Disorder (CGI-BP-M) (Vieta et al., 2002), all assessments were conducted at the same visit. At all participating centres, the interviewers were senior clinical mood disorder psychiatrists. The group of healthy subjects were administered the questionnaires following the same procedure as with the groups of patients; for healthy subjects the assessment included a comprehensive medical history and a screening for psychiatric disorders.

Clinical remission was defined as stability of the mood disorder in the last 6 months and verified by standard psychometric techniques for all patients, as a score of 6 or less on the Young Mania Rating Scale (YMRS) (Colom et al., 2002), and a score of 8 or less on the Hamilton rating scale for depression (HRSD) (Ramos-Brieva and Correro, 1986). This definition of remission has been used and validated in several previous studies (Vieta et al., 2001a, 2001b). To be enrolled, patients had to be in remission for at least 6 months as assessed with the CGI-BP-M (Vieta et al., 2002).

After informing the participants and obtaining their consent, the investigators recorded their sociodemographic and clinical variables, administering the YMRS, HDRS-17 and CGI-BP-M to confirm the stability of the patient’s condition and the absence of psychopathology for healthy subjects.

HRSD total scores were compared between the four different groups. Also, the presence of specific symptoms between subject groups, as evaluated by this scale (classified each symptom as either “present” or “absent”), was analysed. Likewise, for BD patients, the relationship between the depressive symptoms observed, i.e. HDRD total score, and the most recent type of mood disorder episode suffered by the patient (classified either as
A depressive episode or other type was investigated. The relationship between depressive symptoms and the course of the disease was also analysed. Data related to BD groups, BD type I and BD type II, is presented as pooled data (BD). We used the Kruskal Wallis non-parametric test to study the differences in the total HRSD score obtained and the Mann Whitney U test to study the contrasts. Bonferroni’s correction was applied for multiple comparisons. To compare proportions, groups were analysed by the chi-square test, or Fisher’s test when the former was not possible. The relationship between the subsyndromal symptoms of BD patients and prior episode was studied by the biserial correlation coefficient between the HRSD score and diagnosis of precedent episode, classified either as depressive episode or other, this comprising hypomanic, manic or mixed episodes. Spearman’s correlation coefficient (a non-parametric test) was used to study the relationship between subsyndromal symptoms i.e. HDRS total score and the time since onset of disease. Logistic regression models were used to test the predictive value of HRSD items in relation to diagnosis (BD I, BD II and MD); the following factors were used to adjust the regression models, duration of illness, polarity of the most recent acute episode (either depressive or manic–hypomanic), and gender.

### 3. Results

UD patients under clinical remission exhibited the highest HRSD scores with a mean value of 3.4 (±2.3). For the rest of the study groups, the HRSD mean scores were 2.2 (±2.3) for the BD group and 1.2 (±1.4) for the CS group. These differences were significant. Patients with UD under remission presented higher HRSD scores than the BD patients (p=0.006) and healthy subjects (p<0.000). Also, compared to healthy subjects, BD patients under remission presented higher HRSD scores (p=0.001).

When considering the presence or absence of each of the individual symptoms evaluated by the HRSD scale, it was found that patients with BD, as well as patients who have suffered from UD, continue to present residual depressive symptoms during the remission periods (Fig. 1). Indeed, both BD and UD patients in...
remission exhibited symptoms in nearly half of the areas assessed by the HRSD scale; in other words, we observed statistically significant differences between all three groups in 8 out 17 items. The symptoms more strongly associated with a clinical diagnosis of either UD or BD were Depressed Mood, Somatic Anxiety (p<0.0001), Impact on Work and Activities, Psychic Anxiety, Gastrointestinal and Somatic Symptoms (p<0.001), Retardation during the Interview and Genital Symptoms (p<0.05).

Furthermore, when comparing the presence or absence of symptoms between the UD and BD groups, Somatic Anxiety followed by Gastrointestinal Symptoms, Depressed Mood and Psychic Anxiety were more commonly found among patients in remission of an UD episode than in patients with BD.

On the other hand, Retardation during the Interview and Agitation, symptoms usually described to be more common in BD than UD patients, were found in our study to be present with the same frequency in the two patient groups.

Our data shows no relationship between the type of prior episode suffered by the BD patients and the depressive symptoms detected in the patient during clinical stability (r=0.27005).

The length of duration of the symptoms was 15.5 (±10.9) years in the patients with BD. No relationship was observed between the duration of the disorder and the depressive symptoms recorded in the HDRS (r=0.16961).

Multiple logistic regression was used to find which HDRS symptoms were independent predictors of each patient group (BP-I versus BP-II, BP-II versus MD and BP-I versus MD). Among the most frequent HDRS symptoms (i.e. Depressed Mood, Feelings of Guilt, Insomnia Early, Insomnia Middle, Insomnia Late, Work and Activities, Retardation, Psychic Anxiety, Somatic Anxiety, Somatic Symptoms) the significant independent predictors in the two out three of models resulted to be Somatic Anxiety and Depressed Mood. The logistic regression model that was built with the groups BP-I versus BP-II could not find any statistically significant differential item.

The final model for BP-II versus MD, included Somatic Anxiety OR = 0.199, 95% CI (0.075 to 0.528), p=0.0012, showing that the absence of somatic anxiety increases 5-folds the probability of a BP-II diagnosis in a cross-sectional design.

The final model for BP-II versus MD, included both Depressed Mood OR = 0.265, 95% CI (0.096 to 0.733), p=0.0105 and Somatic Anxiety OR = 0.181 95% CI (0.066 to 0.492), p=0.0008; showing that the absence

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**Fig. 1.** Number of individuals (%) by group showing symptoms as assessed by the HDRS. “Symptoms are classified as either “present” or “absent”. Statistically significant differences between all three groups in 8 out 17 items (Depressed Mood, Somatic Anxiety, Impact on Work and Activities, Psychic Anxiety, Gastrointestinal, Somatic Symptoms, Retardation during the Interview and Genital Symptoms) were observed. As shown in the figure, certain symptoms are more frequent among MD patients than BD patients during clinical remission: Somatic Anxiety, Gastrointestinal Symptoms, Depressed Mood and Psychic Anxiety (* p<0.05, ** p<0.01, *** p<0.000). HC, Healthy Control Subjects; BD, Bipolar Disorder Patients; MD, Major Depression Patients.
of Depressed Mood or Somatic Anxiety increase 3.8- and 5.5-folds respectively the probability of a BP-I diagnosis in a cross-sectional design.

4. Discussion

The results of this post-hoc analysis of data from the EDHIPO study show that patients with bipolar disorder I and II considered to be clinically stable both by clinical impression and after an evaluation with standard psychometric instruments, continue in fact to present depressive symptoms such as Depressed Mood, Somatic Anxiety, Impact on Work and Activities, Psychic Anxiety, Gastrointestinal and Somatic Symptoms, Retardation during the Interview and Genital Symptoms. These, although not as severe as during an acute episode, may have an impact on both the patient’s overall condition and performance in daily functioning, as shown in recent publications (Altshuler et al., 2006; Martinez-Aran et al., 2007).

Although no clear set of subsyndromal symptoms present in BD patients under remission, different to that of UD patients, was found, Somatic Anxiety, Gastrointestinal Symptoms, Depressed Mood and Psychiatric Anxiety were more common in the latter, thus providing some clues about the possible diagnosis of a patient seen following a mood episode.

During routine follow-up visits, therefore, attention should be paid to such symptoms, even when the patient is apparently clinically stable, in order to minimise their possible impact on the patient’s quality of live and general functioning. When considering the symptoms of these patients, a detailed study of the clinical profile may reveal some features that may help to establish or confirm a diagnosis.

In this direction, future research should consider that our results in the present study are affected by the design, i.e. the proportion of cases with the diagnoses under study was established beforehand for research purposes. In our study either MDD patients and healthy subjects are likely to be underrepresented. We studied groups of patients/healthy subjects of equal size, but rather than this, to have more precise and epidemiologically meaningful results, the sample sizes should ideally be based on the prevalence figures of each studied condition.

Despite limited effect size, our results are relevant for the routine clinical practice in psychiatry during ambulatory follow-up visits. At specialized clinical settings, clinicians should appraise the diagnosis of patients already identified as UD, when BD is suspected due to either clinical course, family history or to clinical symptom profile during remission periods. Our findings aim to be a contribution towards this appraisal, by increasing the knowledge and by contributing to clinician’s sensitivity to this phenomena. Clinicians should probe for history of hypomania when symptoms that are highly frequent in UD patients under remission, like Somatic Anxiety, Gastrointestinal, Depressed Mood or Psychiatric Anxiety, otherwise are absent in a patient during follow-up visits.

In conclusion, subsyndromal depressive symptoms are common in patients with mood disorders even in those who are apparently well. During clinical remission periods, in general, UD patients showed higher scores on the depression questionnaires than BP and most residual symptoms. Specifically, we have noticed certain symptoms more frequently represented among UD patients than BD subjects; patients suffering from BD may show subsyndromal symptoms with a different profile than those frequently showed by patients suffering from MD. In BP those subsyndromal symptoms seem to be equally present irrespective of the duration of the disease or the polarity of the most recent acute episode — either depressive or manic–hypomanic. The persistence of subthreshold depressive symptoms may explain the gap between syndromal recovery and functional recovery.

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Conflict of interest

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