# Detection of Subclinical Depression in Bipolar Disorder: A Cross-Sectional, 4-Month Prospective Follow-Up Study at Community Mental Health Services (SIN-DEPRES)

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***Objective:*** The aim of this study was to assess the prevalence and the impact of depressive symptoms on the functional outcome of bipolar disorder outpatients in remission.

***Method:*** A cross-sectional, prospective 16-week study of a cohort of 739 euthymic bipolar disorder patients (*DSM-IV-TR* criteria) recruited by 94 investigators was conducted. Clinical stability was assessed at baseline and at week 16 with the modified Clinical Global Impressions Scale-Bipolar Version, and depressive symptoms were assessed at baseline with the 17-item Hamilton Depression Rating Scale (HDRS-17 [primary endpoint measure]), the Montgomery-Asberg Depression Rating Scale (MADRS), and the self-applied Center for Epidemiologic Studies-Depression Scale (CES-D). Functional status was evaluated with the Social and Occupational Functioning Assessment Scale (SOFAS) and Social Adaptation Self-evaluation Scale (SASS). The study was conducted from April 2006 to March 2007.

***Results:*** Subclinical depressive symptoms (SDS) were detected on the HDRS-17 in 16.9% of the sample. In symptom-free patients, the incidence of new SDS after 16 weeks was 20% (MADRS score > 7). At baseline, SDS patients compared to non-SDS patients presented with poorer social-occupational performance (SOFAS score mean difference, −11.9; 95% CI, −14.2 to −9.6) and poorer social adjustment (SASS score mean difference, −5.6; 95% CI, −7.1 to −4.1). Depressive symptoms were inversely related to functional status and social adjustment: MADRS-SOFAS correlation coefficients, $r = -0.54$ ($P < .0001$), and MADRS-SASS correlation coefficients, $r = -0.42$ ($P < .0001$). The self-applied survey identified additional cases with depressive symptoms, showing an SDS total prevalence of 44.9%.

***Conclusions:*** Depressive symptoms in apparently remitted bipolar disorder outpatients are not rare and result in a decline in occupational outcome and social maladjustment.

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Several studies have documented the persistence of substantial depressive residual symptoms among patients diagnosed with unipolar or bipolar depression receiving pharmacologic treatment. The first studies documenting the prevalence rates of these symptoms were published in the 1990s in patients receiving maintenance treatment with lithium, thus this information was available before the introduction of other mood-stabilizing agents.[1] Subsequently, residual depression symptom figures close to 45% were published among patients who suffered bipolar depression and 43% in unipolar depression.[2,3] Furthermore, it has been documented that patients diagnosed with bipolar disorder can spend a third of the year with depressive symptoms, despite receiving appropriate treatment and follow-up.[4]

The predominantly depressive nature of bipolar disorder, as shown in large-scale prospective cohort studies, is now accepted: the National Institute of Mental Health (NIMH) study, with a 20-year follow-up, showed that patients with bipolar I or II disorder primarily presented depressive symptoms of moderate or subclinical severity, which predominated over manic or hypomanic symptoms.[5–7] At the same time, the Stanley Foundation Bipolar Network, using daily records for 1 year, found that ambulatory patients spent 3 times as much time depressed as they did with hypomanic or manic symptoms.[8] Furthermore, a chart-review study every 2 months for 3 years showed that, with respect to more severe symptoms, subclinical symptoms of any polarity were present twice as much over time.[9]

The presence of residual symptoms has been shown to be clearly related to the natural course of the condition: time of disease course and number of recurrences. Therefore, these factors have important implications for the prevention of relapse, as their predictive values indicate.[10–13]

Besides this significant role in relation to relapse prediction, the association of residual symptoms and their functional impact on a patient's life has also been described.[14,15] Patients with subclinical depressive symptoms present 3 to 6 times more functional impairment in various domains, such as work, housework, and relationships with relatives and friends, than those who do not have these symptoms.[13]

Therefore, the importance of identifying and appropriately treating these symptoms is widely acknowledged so that patients can obtain complete disease remission and thus improve their clinical outcomes in both the medium and long term.[12]

The relevance of subclinical symptoms led us to conduct a similar study to the ones that have already been conducted but in a community health services setting, with the primary objective of obtaining a cross-sectional estimation of the subclinical depressive symptoms (SDS) present among symptomatically stable patients who are regularly cared for

in the community. The objective was to investigate the prevalence of subclinical depressive symptoms in a large group of patients with a diagnosis of clinically stabilized bipolar disorder (types I and II) and to follow up with that cohort of patients to observe their outcome and the impact the depressive symptoms had on their functioning.

## METHOD

This was a prospective 16-week epidemiologic study of a cohort of consecutive outpatients with clinically stable bipolar disorder. The study was conducted in 88 community-based mental health centers and private psychiatric outpatient clinics across several Spanish regions.

### Subjects

Patients over 18 years of age with a well-established diagnosis of bipolar disorder according to *DSM-IV-TR* criteria,[16,17] who had remained clinically stable for at least the last month, were eligible for this study. *Clinical stability* was defined as a "normal" or "minimal" disturbance score on the depression and mania items of the modified Clinical Global Impressions Scale-Bipolar Version (CGI-BP-M).[18,19] Only patients who had suffered at least 1 acute episode in the 5 years prior to inclusion in the study were enrolled. Patients were excluded if no reliable information was available at the center; they presented acute depression, mania, hypomania, or mixed symptoms at inclusion; they suffered from another serious and active psychiatric condition, drug addiction, other conditions affecting the central nervous system, or organic brain disease; or they had suffered any brain trauma, dementia, or an uncontrolled serious medical condition or illness that could produce secondary depression (eg, hypothyroidism). We also excluded first-episode patients and those participating in clinical trials.

At each center, healthy volunteer subjects were also selected from clinics other than the psychiatric department to become members of the control group. These subjects had to have no members of patient's family or staff from the psychiatric department. Patient inclusion was consecutive at each center; healthy voluntary subjects were the last recruited cohort (ie, 1 patient per center). The study was conducted from April 2006 to March 2007.

The study was approved by the Independent Ethics Committee of 1 of the participating centers, the Hospital Clinic of Barcelona.[20] All participants were informed about the study and provided their written informed consent prior to inclusion.

### Procedure

The study objective and data processing procedures were explained to all the subjects. After obtaining their written informed consent, the investigators obtained the study data by means of a clinical interview and psychiatric examination. The interview obtained information about sociodemographic and clinical data (including history of psychiatric disorders in first-degree relatives) and treatments received and also the degree of compliance and satisfaction with them. The presence of depressive symptoms and the patient's social-occupational status and functional performance in different aspects of his/her life were also assessed.

Participants, except the healthy control subjects, were reassessed at a second visit after 16 weeks (± 4 weeks) regarding to the intensity of depressive symptoms, clinical worsening occurring during the study period, and important life events that occurred and which could have affected the patient and the use of health care resources.

### Clinical Assessment

To determine the stability of the condition at baseline visit, all the patients were evaluated with the CGI-BP-M[18,19]; the 17-item Hamilton Depression Rating Scale (HDRS-17)[21,22] was also administered to describe any present depressive symptoms and their severity at the time patients were included in the study. The course of symptoms was likewise recorded using the Montgomery-Asberg Depression Rating Scale (MADRS)[23,24] administered at enrollment and at the end of the study.

The patient group with depressive symptoms was defined according to the baseline result in the HDRS-17 scale (total score). Prevalence of depressive symptoms was thus defined as the percentage of patients who obtained a total score indicating "mild depression" (score 7 to 17) on the HDRS-17 scale. The subclinical depression status of the patients, divided into 2 groups (SDS or non-SDS), was defined by the specified score range on this scale (SDS = HDRS-17 score between 7 and 17, non-SDS = HDRS-17 score < 7).

Depressive symptoms referred by subjects themselves were obtained as supplementary information (eTable 1). We administered the Center for Epidemiologic Studies Depression Scale (CES-D),[25,26] a widely used instrument to detect cases of depression in the general population.[27] The frequency, but not the intensity, of depressive symptoms reported by the subject in the week before the visit was also evaluated.

### Evaluation of Functional Status

To evaluate the impact of the condition on the patient's social-occupational life, the Social and Occupational Functioning Assessment Scale (SOFAS)[17] was used; a cut-off score of 70 or more defined good social-occupational performance.

The impact of the condition on the patient's social life was evaluated by means of the Social Adaptation Self-evaluation Scale (SASS).[26,28–30] This is a self-applied scale used in depression studies to measure social behavior and motivation, revealing the patient's perception of his/her functional status according to different roles and functional areas.

### Data Analysis

The sample size was established in order to determine the prevalence of the SDS, reported to be around 45%.[2] The estimation of the 95% confidence interval (CI) was considered with a level of imprecision not higher than 8%. For sample size calculations, it was also estimated that 10% of patients



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would provide invalid data and that 6% would be lost to follow-up, as was reported in previous publications.[31] Control group size was calculated to detect differences on HDRS-17 scale total score between healthy subjects and bipolar disorder subjects based on previously reported local rates[32] and the expectation of recruiting one control subject per center.

Patients' mean total scores on the HDRS-17 were compared with the results obtained from the control group using a Student *t* test, excluding item 16, addressed to score insight. The association between clinical factors prior to inclusion and the presence of baseline depressive symptoms (HDRS-17 as dependent variable) was explored using a linear regression model including "duration of clinical stability" and "polarity of most recent episode" factors.

Results on the HDRS-17, which determined the prevalence of SDS, were combined with the results obtained by the self-applied CES-D questionnaire, on which a score of over 15 was considered a possible case of SDS. With this information, the total prevalence of baseline SDS in the sample (ie, total SDS) was defined as the SDS rate detected by either of the 2 instruments. The degree of consistency between the 2 instruments, HDRS-17 and CES-D, was analyzed by a consistency analysis using calculations of the κ statistic.

In order to qualitatively characterize the patients with a positive result for SDS by only the self-applied test (CES-D), these patients were compared with patients who obtained a positive result for SDS with both instruments with regard to their sociodemographic and clinical variables and to their results on the CES-D and SASS scales, using a $\chi^2$ or Student *t* test, as appropriate.

The incidence of new SDS was determined in patients free of depressive symptoms at the baseline assessment and who had no recurrences during follow-up. The incidence of SDS was defined in 2 ways: (1) the proportion of patients presenting with clinically significant increases on the MADRS scale (an increase of at least 50% on this scale relative to the baseline score resulting in a final score of more than 7) and (2) the proportion of patients who obtained a score of more than 7 on this scale at the end of follow-up.[33]

All the statistical tests were performed considering a significance level of 5%. No corrections were made for multiple comparisons, and any difference was considered in order to increase the possibility of finding differences.[34] The SAS statistical package, release 8.2 (SAS Institute Inc, Cary, North Carolina), was used for all statistical analyses.

## RESULTS

The study included 761 consecutive bipolar disorder patients, 739 of whom were included in the analysis. Those excluded (n = 22) were deviations from the protocol due to failing to meet the stability criteria (CGI-BP-M), having presented less than 1 acute episode in the last 5 years, or presence of another medical condition such as hypothyroidism. The group of healthy volunteers comprised 91 subjects. Table 1 describes the sociodemographic and clinical characteristics of all study subjects. The majority of bipolar disorder patients were type I (n = 537, 72.7%), with only 27.3% type II (n = 202).

Most bipolar disorder patients had suffered at least 1 depressive episode in the past (88%, n = 652), although this was the most recent episode in only half of cases (52%, n = 377).

### Subclinical or Mild Depression Detected by Clinical Interview

Subclinical depressive symptoms were detected in 125 of 739 cases (16.9%). The population adjustment did not provide additional information resulting in similar percentages (17.4%; 95% CI, 14.7%–20.1%). The observed SDS rates were similar in bipolar I disorder (15.9% [n/n = 82/537]; 95% CI, 12.8%–19.0%) and bipolar II disorder (21.4% [n/n = 43/202]; 95% CI, 15.7%–27.1%), whereas the highest percentage of SDS was found among rapid cycling patients, with 28.6% of patients with SDS (n/n = 34/126; 95% CI, 20.7%–36.5%). Table 1 shows the sociodemographic and clinical characteristics of the entire sample according to SDS status (SDS or non-SDS). Table 2 shows the results obtained at baseline clinical examination and at the end of the study.

Figure 1 shows the HDRS-17 item-by-item severity analysis according to SDS status; in all symptoms evaluated, the depressive symptoms presented by SDS patients had greater severity than those of the non-SDS patients.

Both groups, SDS and non-SDS, were comparable with regards to sociodemographic and clinical characteristics, except for time since the last episode and duration of clinical stability. The last episode occurred approximately 1 year before enrollment among SDS patients. Compared with non-SDS patients, SDS patients' last episode was more recent, with a mean difference of around 4 months between both groups (95% CI, 33–205 days); clinical stability was therefore shorter in the SDS group. The linear regression analysis confirmed that duration of clinical stability was inversely related to the severity of the depressive symptoms recorded upon inclusion in the study, showing a significant association between time since the end of a previous episode and the baseline HDRS-17 score; for each month elapsed since the last episode, the HDRS-17 score was lower (coefficient of regression = 0.04, $P < .0001$). Finally, when the previous episode was manic, this was associated with a less severe baseline depressive symptoms score (coefficient of regression = 0.86, $P = .0021$), unlike other types of episodes that did not present a significant association. This regression model containing both parameters explained only 5% of the variability.

The mean score difference on the HDRS-17 found between the bipolar disorder and control subject groups was 2.7 points (95% CI, 1.4–2.8), with bipolar disorder patients having higher scores than the control subjects (Table 2). Control subject participants were slightly younger than bipolar disorder patients (mean age difference, 3.9 years; 95% CI, 1.1–6.9) and had a higher level of education: 44% of control subjects had a university degree versus 21.9% in the bipolar disorder group.

Table 1. Descriptive Sociodemographic and Clinical Data on the Entire Study Sample, and by Groups According to SDS Status[a] at Study Inclusion

| | Bipolar Disorder | | | | | | Healthy Subjects (n = 91) | |
|---|---|---|---|---|---|---|---|---|
| | Total (n = 739) | | Non-SDS (n = 614) | | SDS (n = 125) | | | |
| Variable | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| Age, y | 46.1 | 13.7 | 46.0 | 13.7 | 46.5 | 13.5 | 42.1 | 11.6 |
| | n | % | n | % | n | % | n | % |
| Gender | | | | | | | | |
| Male | 295 | 39.9 | 247 | 40.2 | 48 | 38.4 | 31 | 34.1 |
| Female | 438 | 59.3 | 362 | 59.0 | 76 | 60.8 | 60 | 65.9 |
| Marital status | | | | | | | | |
| Married/stable partner | 380 | 51.4 | 314 | 51.1 | 66 | 52.0 | 64 | 70.3 |
| Single | 234 | 31.7 | 199 | 32.4 | 35 | 28.0 | 20 | 22.0 |
| Other situation | 120 | 16.2 | 97 | 15.8 | 23 | 18.4 | 6 | 6.6 |
| Education level | | | | | | | | |
| No education completed | 47 | 1.9 | 41 | 6.7 | 6 | 4.8 | 0 | 0 |
| Basic education | 279 | 37.8 | 221 | 36.0 | 58 | 46.4 | 11 | 12.1 |
| High school | 386 | 31.9 | 197 | 32.1 | 39 | 31.2 | 39 | 42.9 |
| University | 162 | 21.9 | 142 | 23.1 | 20 | 16.0 | 40 | 44.0 |
| Paid occupational status (yes) | 291 | 39.4 | 238 | 38.8 | 53 | 41.7 | … | … |
| Living situation | | | | | | | | |
| Alone | 105 | 14.2 | 89 | 14.5 | 16 | 12.8 | 5 | 5.5 |
| With parents | 177 | 24.0 | 150 | 24.4 | 27 | 21.6 | 13 | 14.3 |
| With spouses/children | 389 | 52.6 | 320 | 52.1 | 69 | 55.2 | 67 | 73.6 |
| Residence, sheltered housing, or other situation | 54 | 7.2 | 44 | 7.1 | 10 | 8.0 | 5 | 5.5 |
| Bipolar disorder subtype | | | | | | | | |
| I | 537 | 72.7 | 455 | 74.1 | 82 | 65.6 | … | … |
| II | 202 | 27.3 | 159 | 25.9 | 43 | 34.4 | … | … |
| Rapid cycling | 126 | 17.1 | 92 | 15.0 | 34 | 27.2 | … | … |
| Past depressive episodes | 652 | 88.2 | 536 | 87.3 | 116 | 92.8 | … | … |
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| Time elapsed since last depressive episode, d[b] | 889 | 1,385 | 920 | 1,338 | 749 | 1,581 | … | … |
| Age at first episode, y | 29.7 | 11.8 | 29.9 | 11.9 | 29.0 | 11.3 | … | … |
| No. of episodes per year | 1.5 | 1.1 | 1.4 | 1.1 | 1.7 | 1.3 | … | … |
| Time elapsed since last episode, d[c] | 455.4 | 441.3 | 475.1 | 452.1 | 356.6 | 369.3 | … | … |
| Duration of most recent episode, d[d] | 74.1 | 70.3 | 72.5 | 68.6 | 82.1 | 78.0 | … | … |
| Duration of clinical stability, mo[e] | 17.0 | 26.8 | 18.3 | 28.6 | 10.8 | 13.5 | … | … |
| | n | % | n | % | n | % | n | % |
| Type of most recent episode[f] | | | | | | | | |
| Depressed (296.5x) | 377 | 51.8 | 312 | 50.8 | 65 | 52.0 | … | … |
| Manic (296.46) | 184 | 24.9 | 156 | 25.4 | 28 | 22.4 | … | … |
| Hypomanic (296.40) | 127 | 17.2 | 108 | 17.6 | 19 | 15.2 | … | … |
| Mixed (296.6x) | 46 | 6.2 | 33 | 5.4 | 13 | 10.4 | … | … |
| Unspecified (296.7) | 4 | 0.5 | 4 | 0.7 | 0 | … | … | … |
| Life events since last assessment | 118 | 16.0 | 94 | 15.3 | 24 | 19.2 | 23 | 25.3 |
| Psychiatric comorbidity (ongoing) | | | | | | | | |
| Substance abuse | 109 | 14.7 | 94 | 15.3 | 15 | 12.0 | … | … |
| Panic attack | 50 | 6.8 | 40 | 6.5 | 10 | 8.0 | … | … |
| Anxiety disorders, not specified | 48 | 6.5 | 37 | 6.0 | 11 | 8.8 | … | … |
| Family history | | | | | | | | |
| Depressive disorder | 254 | 34.4 | 209 | 34.0 | 45 | 36.0 | … | … |
| Bipolar disorder | 139 | 18.8 | 120 | 19.5 | 19 | 15.2 | … | … |
| Substance abuse | 58 | 7.8 | 47 | 7.7 | 11 | 8.8 | … | … |
| Psychotic disorder-schizophrenia | 50 | 6.8 | 36 | 5.9 | 14 | 11.2 | … | … |

[a]SDS status was defined as a 17-item Hamilton Depression Rating Scale total score between 7 and 17 at baseline assessment. Within the SDS group, there was a higher rate of bipolar II disorder patients (a difference of nearly 10% compared to the non-SDS group). There was also a higher rate of rapid cycling patients among the SDS group compared to those in the non-SDS group; the difference was 12%.

[b]n = 652, patients with past history of any depressive episode. Median values for this variable were 449 days for the bipolar disorder group, 499 days for the non-SDS group, and 299 days for the SDS group.

[c]Median values for this variable were 280 days for the bipolar disorder group, 305 days for the non-SDS group, and 228 days for the SDS group.

[d]Median values for this variable were 60 days for the bipolar disorder group, 60 days for the non-SDS group, and 60 days for the SDS group.

[e]Median values for this variable were 9 months for the bipolar disorder group, 10 months for the non-SDS group, and 6 months for the SDS group.

[f]With *DSM-IV* codes.

Abbreviation: SDS = subclinical depressive symptoms.

### Self-Reported Depressive Symptoms and Prevalence of Total SDS

The percentage of patients with scores showing mild depression on the CES-D scale was similar to the percentage of patients detected by clinical interview: 15.5% (n/n = 113/739; 95% CI, 12.8%–18.0%). However, unlike the results obtained with the HDRS-17 scale, an additional group of patients were identified as having moderate-severe depression in this self-applied questionnaire (ie, a score of 21 or more). Added to the other group, a total of 40% of the cases had depressive symptoms (297 of 739) according to the self-applied questionnaire. The 2 detecting methods (ie, HDRS-17 and CES-D) were concordant in 92 of 739 bipolar disorder patients, whereas 205 additional cases were identified with the self-applied questionnaire. The resulting κ consistency coefficient was 0.25 (95% CI, 0.19–0.32; $P < .0001$), which is considered slight to acceptable.[35] Therefore, with the 2 assessment tools, 44.9% (n = 332) of bipolar disorder patients studied presented some degree of depressive symptoms identified by either method (total SDS).

Table 3 shows the results from comparing the patients who were detected only by the self-applied test with those detected by both methods. Both groups were comparable with regards to sociodemographic and clinical characteristics. The analysis of the CES-D scale factors showed that, although these patients had similar results in relation to somatization and interpersonal relations as those detected by the clinician, patients who were detected only by the self-applied test presented a lower depressed mood, irritability and despair component, and a greater positive mood component. SASS scale factors showed that the patients who were detected only by the self-applied test, although exhibiting better social adjustment results, showed less capacity for enjoyment/less interest in their main activity as indicated by the analysis of those SASS items related to interest in activities.



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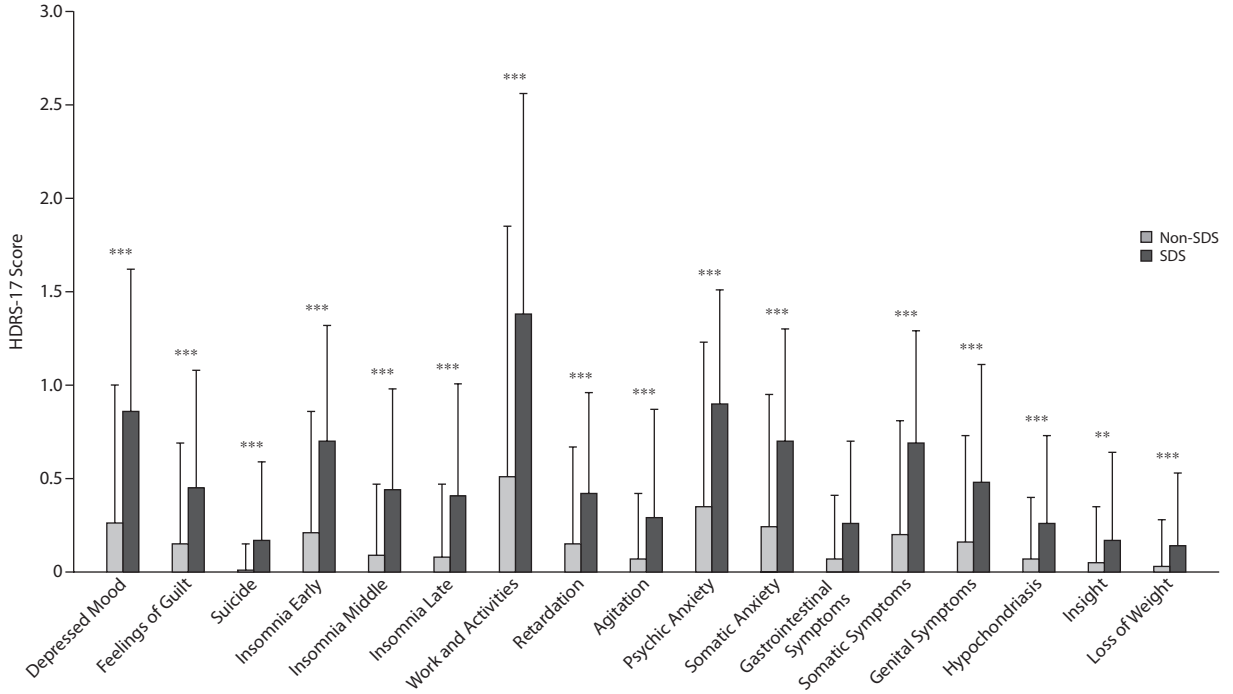
**Table 2. Baseline Results of Clinical Assessment for All Participants and by Bipolar Disorder Patient Groups According to SDS Status[a]**

| | Healthy Controls (n = 91) | | Bipolar Disorder[b] (n = 739) | | Non-SDS Subgroup (n = 607) | | SDS Subgroup (n = 125) | | Mean Difference[c] | |
|---|---|---|---|---|---|---|---|---|---|---|
| Assessment | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | 95% CI |
| HDRS-17 | 1.9 | 2.2 | 3.7 | 3.1 | 2.7 | 2.2 | 8.7 | 2.1 | 6 | 5.6 to 6.4 |
| MADRS | 1.8 | 2.5 | 4.9 | 4.5 | 3.6 | 3.3 | 10.8 | 4.9 | 7.2 | 6.5 to 7.9 |
| CES-D[d] | 6.6 | 5.7 | 15.2 | 9.9 | 13.8 | 9.3 | 22.0 | 9.7 | 8.2 | 6.3 to 10.0 |
| Assessment of social and occupational functioning | | | | | | | | | | |
| SOFAS[e] | 93.3 | 5.6 | 79.5 | 12.7 | 81.5 | 11.5 | 69.6 | 13.2 | −11.9 | −14.2 to −9.6 |
| SASS[e,f] | … | … | 37.5 | 7.9 | 38.5 | 7.6 | 32.9 | 7.8 | −5.6 | −7.1 to −4.1 |
| | n | % | n | % | n | % | n | % | % | 95% CI |
| Use of health resources[g] | | | | | | | | | | |
| Psychiatry outpatient visits | … | … | 684 | 92.6 | 564 | 91.9 | 120 | 96.0 | 4.1 | 0.9% to 9.9% |
| Psychology outpatient visit | … | … | 340 | 46.0 | 61 | 9.9 | 31 | 24.8 | 14.1 | 7.0% to 22.8% |
| General practitioner visit | … | … | 92 | 12.4 | 269 | 43.8 | 71 | 56.8 | 13.0 | 3.5% to 22.5% |
| Hospital admissions at psychiatric specialized units | … | … | 135 | 18.3 | 100 | 16.3 | 35 | 28.0 | 11.7 | 3.3% to 20.1% |

[a]Results are based on the answers of the patients to clinical interviews and to self-administered questionnaires at study inclusion.
[b]Mean results obtained by all bipolar disorder patients at baseline were under the cutoff score for mild depression for all the used scales, ie, HDRS-17, MADRS, and CES-D.
[c]A positive mean difference indicates that the SDS group had a higher result in the studied variable.
[d]CES-D scale is commonly used as an indicator of symptoms related to depression; high scores on CES-D (from a score of 16) address the need for a more in-depth analysis of the patient's clinical status.
[e]For SOFAS and SASS scales, a higher score means a better social and occupational functioning; therefore, score reduction on these scales indicates a worsening of this variable. Mean results on the SOFAS scale for bipolar disorder patients showed mild deterioration of social/occupational functioning, ie, slight impairment in social, occupational, or school functioning.
[f]A score between 35 and 52 is considered normal, while scores lower than 25 are considered as indicators of social maladjustment (Bobes[28]).
[g]At baseline visit the use of health resources within the year before inclusion was recorded, and resources used during the study period were recorded at the final study visit.
Abbreviations: CES-D = Center for Epidemiologic Studies-Depression Scale, HDRS-17 = 17-item Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, SASS = Social Adaptation Self-evaluation Scale, SDS = subclinical depressive symptoms, SOFAS = Social and Occupational Functioning Assessment Scale.

**Figure 1. Patients in Clinical Remission: Profile of Depressive Symptoms by Group on the 17-Item Hamilton Depression Rating Scale (HDRS-17)[a]**




[a]Severity of HDRS-17 items on patients with bipolar disorder during an outpatient follow-up visit (n = 739). Clinical profile is displayed according to the presence of subclinical depressive symptoms at baseline assessment (SDS status as a score of 7 or above on HDRS-17) (SDS, n = 125, versus non-SDS, n = 614). Differences are observed for all items among both groups. SDS patients showed more severity in all items. The higher intensity for the SDS group was observed on depressed mood (item 1), impact on work and activities (item 7), and psychic anxiety (item 10).
**$P < .001$.
***$P < .0001$.
Abbreviation: SDS = subclinical depressive symptoms.



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### Change in SDS Status, Course of Depressive Symptoms, and Incidence of SDS During Follow-Up

The prospective 16-week follow-up involved 663 bipolar disorder patients (90% of the baseline sample). The MADRS score corresponding to the baseline cutoff point defined in the HDRS-17 scale was 8.5, as estimated by linear regression. This regression model solely comprising the HDRS-17 scale explained 62.5% of the variability. According to this cutoff point, over half of the patients with subclinical depression at baseline (60%, n = 66) changed their SDS status after 16 weeks, with depression symptoms remitting to normal. Mean global reduction of symptoms in the SDS group at the end of follow-up was –3.3 points on the MADRS scale (95% CI, –4.4 to – 2.4). A higher use of health care resources was also seen in the group of patients with depressive symptoms (Table 2).

Regarding the incidence of SDS, 12% of the non-SDS cases (58 of 502) suffered increases in the depressive component meeting the established criteria for clinical significance, and 6% (n = 32) reported new affective episodes during follow up. As a summary measure, 20% of the bipolar disorder patients with a status of non-SDS at baseline obtained scores corresponding to mild depression in the MADRS scale at the end of the study.

An increase in depressive symptoms was found in patients registering an important life event during follow-up (n = 106, 16%; with a mean [SD] increase in MADRS score of 3.7 [7.9] points; 95% CI, 2.2–5.3), which was at variance with those registering no such events (n = 606, 84%), who showed little variation (mean [SD] –0.02 [4.7]; 95% CI, –0.4 to 0.4); the mean observed difference among both groups was 3.8 points on MADRS (SD = 5.3; 95% CI, 2.6–4.9; $P < .0001$).

Table 3. Characterization of the Patients With SDS Detected by Clinician-Administered and Self-Applied Instruments: Depressive Symptomatology and Social Adjustment Factors (n = 739)

| | Method for SDS Detection | | | | |
|---|---|---|---|---|---|
| | Both Methods (n = 92)[a] | | Only Self-Applied (n = 205) | | |
| Instrument | Mean | SD | Mean | SD | *P* Value |
| CES-D[b] | | | | | |
| Factors[c] from Soler et al[25] | | | | | |
| Factor 1: depressed mood | 8.9 | 3.5 | 7.7 | 3.4 | < .01 |
| Factor 2: positive mood | 3.8 | 1.1 | 3.4 | 1.2 | < .01 |
| Factor 3: irritability-hopeless feelings | 1.7 | 1.0 | 1.2 | 1.0 | < .01 |
| Factor 4: interpersonal social | 2.0 | 1.5 | 1.8 | 1.5 | .34, NS |
| Factors[d] from Joseph and Lewis[36] | | | | | |
| Factor 1: depressed affect—bothered, blues, restless, happy, talked less, lonely, enjoyed life, crying spells and feeling sad | 7.9 | 2.5 | 7.0 | 2.5 | < .05 |
| Factor 2: somatic disturbance—depressed, exhausted, fearful, sleep disturbance and low energy level | 4.5 | 1.9 | 4.1 | 1.9 | .11, NS |
| Factor 3: positive affect and self-worth—good as others, hopeful, feelings of failure, happy and enjoyed life | 3.9 | 1.1 | 3.5 | 1.2 | < .05 |
| Factor 4: interpersonal difficulties—sleep disturbance, talked less, people unfriendly and people dislike | 2.5 | 1.6 | 2.2 | 1.5 | .09, NS |
| SASS[e] | | | | | |
| Total score | 31.2 | 7.3 | 34.7 | 7.7 | .001 |
| Work interest (item 1)[f] | 2.1 | 1.0 | 1.7 | 0.8 | .012 |
| Interest in hobbies (item 2)[f] | 2.6 | 0.9 | 2.4 | 0.9 | .10, NS |
| Enjoyment of principal activity (item 3) | 2.9 | 0.7 | 2.6 | 0.8 | .04 |
| Factors from Bosc[37] | | | | | |
| Factor 1: functioning on external relationships | 9.3 | 2.6 | 10.3 | 2.6 | .005 |
| Factor 2: functioning on job and leisure | 8.9 | 2.4 | 9.9 | 2.5 | .0092 |
| Factor 3: social and intellectual interests | 6.4 | 2.1 | 7.5 | 2.4 | .0016 |
| Factor 4: familial relationships and behavior strategies | 7.1 | 1.6 | 7.8 | 1.6 | .0005 |

[a]Bipolar disorder patients with SDS status according both methods, ie, HDRS-17 and self-applied CES-D scales.
[b]Higher scores mean more depressive symptoms.
[c]Factor analysis from a sample of outpatients diagnosed of mood disorders under follow-up programs.
[d]Factor analysis from a sample of general population, university students.
[e]Higher scores mean better social adjustment.
[f]Patients were encouraged to answer either item 1 or item 2 in accordance with a paid occupational status (item 1) or other types of principal activities (item 2).
Abbreviations: CES-D = Center for Epidemiologic Studies-Depression Scale, HDRS-17 = 17-item Hamilton Depression Rating Scale, NS = not significant, SASS = Social Adaptation Self-evaluation Scale, SDS = subclinical depressive symptoms, SOFAS = Social and Occupational Functioning Assessment Scale.

### Subclinical Depression and Social-Occupational Impact

The social-occupational performance of bipolar disorder patients showed a slight decline (Table 2), which also remained at the follow-up visit. Greater impairment in baseline functional status was found in the SDS group, involving more difficulties related to social, occupational, or school life.

An inverse correlation between the depression rating and social-occupational performance scales was observed (Table 4), suggesting that depressive symptoms have a negative impact on the patient's social-occupational performance and social adjustment, although it explained only part of the observed variability. In this context, it was also found that, although both scales were significantly correlated, they evaluated different aspects of patients' lives (Figure 2).

## DISCUSSION

The results of the SIN-DEPRES study are consistent with prior studies and confirm the presence of an important subclinical depressive component in patients with clinically stable bipolar disorder. Although these patients receive maintenance treatment, a significant number of them continue to have mild or subclinical symptoms of depression that go unnoticed. What is noticeable from this study, however, is that subthreshold depressive symptoms were quite poorly detected not only by clinical impression (all the patients enrolled were rated as "normal" or "minimally ill" on the CGI-BP-M) but also by widely used rating scales such as the

**Table 4. Correlation Coefficients Between Depressive Symptoms and Social/Occupational Functioning (n = 739)[a]**

| | Depression Scale | | |
|---|---|---|---|
| Social and Occupational Functioning | HDRS-17 | MADRS | CES-D[b] |
| SOFAS[b] | −0.49*** | −0.54*** | −0.42*** |
| SASS total score[b,c] | −0.36*** | −0.42*** | −0.47*** |
| Factors according to Bosc[37] study[d] | | | |
| Factor 1: functioning on external relationships | −0.34*** | −0.41*** | −0.47*** |
| Factor 2: functioning on job and leisure | −0.37*** | −0.43*** | −0.49*** |
| Factor 3: social and intellectual interests | −0.29*** | −0.36*** | −0.35*** |
| Factor 4: familial relationships and behavior strategies | −0.33*** | −0.37*** | −0.45*** |

[a]The results indicates a significant inverted relationship between depressive symptoms and social and occupational functioning. The highest correlation coefficients were obtained between the results from the same rater, either the clinician or the patient. MADRS showed higher correlation coefficients than HDRS-17 to social and occupational functioning measurements. Depressive symptoms as expressed by the patient himself/herself (CES-D) showed a high correlation with patient's functioning on external relationships and on job and leisure factors. The opinion of accompanying people appeared to be more related to the clinician's judgment.

[b]Complementary information was collected from patient's accompanying person from the question, "How often have physical health or emotional problems interfered with social activities (ie, visit friends and family)?" followed by a multiple-choice response. At baseline, correlations with the opinion of the patient's accompanying person was $r = 0.32$, $P < .0001$, for the SOFAS and $r = 0.25$, $P < .0001$, for the SASS, and, at the end of study period, the correlation was $r = 0.45$, $P < .0001$, for the SOFAS and $r = 0.36$, $P < .0001$, for the SASS.

[c]Self-applied scale.

[d]According to the factor structure reported in Bosc.[37]

***$P < .0001$.

Abbreviations: CES-D = Center for Epidemiologic Studies-Depression Scale, SASS = Social Adaptation Self-evaluation Scale, SOFAS = Social and Occupational Functioning Assessment Scale.

HDRS (125 patients of 739, approximately 17%); when self-applied measures were used, 297 of 739 patients reported subclinical depressive features (approximately 40%). Two more patients had depressive symptoms over the threshold of 17 on the HDRS-17 despite being qualified as minimally depressed. Combining clinician-applied and self-applied rating scales, 332 (almost 45%) "euthymic" patients had some degree of depression.

Moreover, at 16-week follow-up, around 20% of patients who were symptom-free at baseline developed mild or subclinical depressive symptoms. This speaks to the high prevalence and burden associated to subclinical symptoms and of our inability to detect and treat them appropriately.

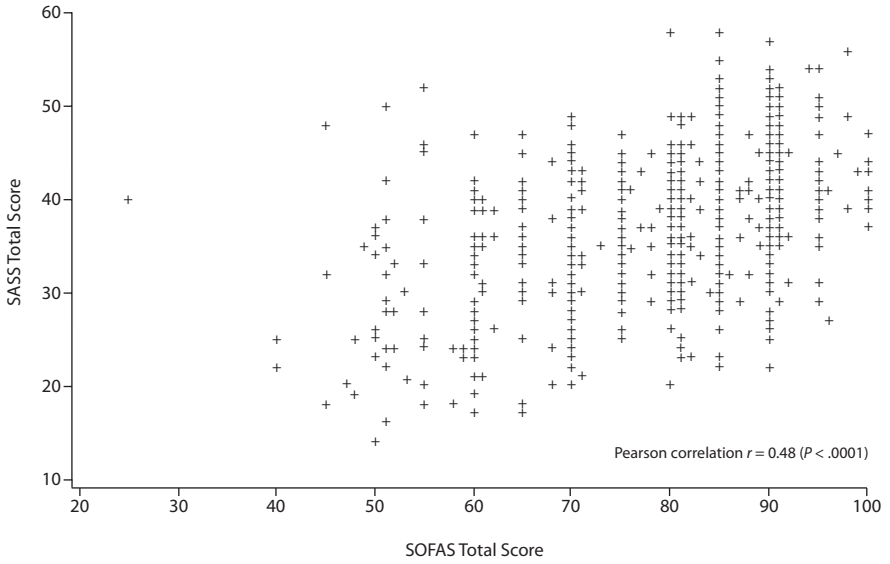
As in other studies, no differences in the prevalence of depressive symptoms between bipolar I and II disorders were observed. In bipolar II disorder, prevalence was slightly higher, although the difference was not statistically significant. Prior studies found that the 2 disorders show similar features, largely characterized by moderate or subsyndromal depressive features during the course of the condition.[5–7] The duration of symptoms in patients was also similar.[14] It is thus confirmed that bipolar II disorder is not a milder form of bipolar disorder but a serious condition, with chronic depressive symptoms that may be much more serious and persistent than what was believed in the past (Vieta et al[38]).

Although there is no consensus on the definition of SDS used in the literature, the results of this study are consistent with published prevalence estimations for subsyndromal depression: Benazzi[2] found residual depressive symptoms in 45% of the evaluated patients with bipolar II disorder, and the Stanley Foundation Bipolar Network study found a prevalence of 38% using the Inventory of Depressive Symptomatology Clinicians Rating.[13] Other studies evaluating symptoms of any polarity have indicated prevalence rates of 26%[15] and, more recently, of 53% in the STEP-BD study.[12] Comparisons between these figures are difficult because of the heterogeneous definitions used across the different studies.[31]

The depressive component identified during the clinical interview seems, at least in some cases, related to last-episode recency (ie, to the duration of clinical stability) as examined in our study, which would be cases showing truly residual symptoms. Depression was more intense in patients who suffered an episode shortly before the control visit and when the episode was not a manic one. However, this model explains only 5% of the variability observed on HDRS-17 baseline scores.

The information about emotional status provided by the patient by self-assessment seems to adequately complement the information obtained from the interview, as already acknowledged by other authors.[33] The CES-D scale was selected in our study because it best evaluates cognitive aspects of depression, whereas previous studies used life chart methods that predominantly evaluate subjective aspects of mood. Moreover, the latter method tends to generate a large volume of data that may be difficult to process (eg, conversion to HDRS scores).[9,14,39,40] The CES-D scale represents a detailed measurement of mood state at a time close to the visit, does not require significant memory effort by the patient, and may therefore be an alternative for complementing mood evaluation by the clinician. Furthermore, as we have observed, this information is specifically correlated with patients' social, occupational, and leisure-related performance. The CES-D is therefore an interesting tool to be considered for evaluating bipolar disorder patients during follow-up visits to detect cases at risk of suffering from subsyndromal depressive symptoms. This scale was designed for epidemiologic studies in the general population and has also been clinically validated in Spain in patients with affective disorders.[25] Patients in the SIN-DEPRES study obtained lower scores (mean = 15.2; SD = 9.9; 95% CI, 14.4–15.9) than those obtained from patients in the validation study (mean = 28, SD = 13), thus indicating a lesser depressed mood component in our sample, which is consistent with the fact that our patients were initially "normal" or "minimally ill"; a weaker correlation between the CES-D and the HDRS-17 scale ($r = 0.46$, $P < .0001$ in SIN-DEPRES versus $r = 0.695$, $P < .0001$) was also found in our study compared to validation study. Similarly, using the same defined cutoff points than the validation study (ie, CES-D score > 15 and HDRS-17 score > 9) we obtained less sensitivity (0.62 versus 0.95) but more specificity (0.87 versus 0.66). According to

**Figure 2. Relationship Between 2 Clinical Methods for the Assessment of Social-Occupational Status, Clinicians Ratings, and Patient Self-Reporting[a]**




[a]On the Spanish validation study of the SASS (Bobes et al[28]), the scale was administered to a sample of patients with a diagnosis of unipolar depression, and construct/criteria validation were assessed using the Global Assessment of Functioning (GAF) scale. The study showed that the theoretical construct assessed by the SASS was different from what is measured by GAF clinical ratings (Pearson correlation was $r = 0.38$). The SOFAS is a measure of social, occupational, and school functioning but not clinical status with a similar rating format as the GAF. The SASS is a scale of behavioral and social motivation in which a score between 35 and 52 is considered normal, while scores below 25 are considered as social maladjustment (Bosc et al[29]).

Abbreviations: SASS = Social Adaptation Self-evaluation Scale, SOFAS = Social and Occupational Functioning Assessment Scale.

the authors, the CES-D scale does not enable quantification of the severity of depressive symptoms[25,26]; however, we were able to qualitatively study in depth the symptoms in a sample of clinically stable patients. Self-applied scales can be useful tools for detecting qualitative aspects of subsyndromal symptoms.

In bipolar disorder patients, besides obtaining clinical stability, it is essential to attain an emotionally positive status. In studies conducted in patients who suffered bipolar depression, besides absence of symptoms, other aspects frequently mentioned to influence duration of remission are the presence of characteristics related to positive mental health, such as optimism and self-confidence, a return to one's usual normal self, and returning to one's usual performance level.[41]

### Subclinical Symptoms and Social-Occupational Performance

The relationship between depressive symptoms and social-occupational performance, showing an expected inverse relationship, was confirmed in our study: ie, the greater the depressive component the worse the performance. Subclinical depressive symptoms evaluated with the HDRS-17 scale are associated with worse psychosocial performance compared with asymptomatic patients.[13,15,42] It has been shown that SDS are closely related to aspects of the patient's performance at work and leisure. The results of our study do not enable us to identify performance areas, as only an overall evaluation was available since this was the project's objective. Future research should delve into these aspects using more specific performance scales such as the Functioning Assessment Short Test[43] in order to design appropriate psychotherapeutic and remediation strategies. The SASS scale was specifically developed to evaluate the efficacy of new antidepressant treatments, and it was validated in the general population and in patients with unipolar depression. Clinical trials indicate that the information provided by the scale during remission is independent from the evaluation performed with depressive symptom intensity scales.[37] This construct independence, with the HDRS-17 scale, was confirmed, for example, in the Spanish validation study; the authors found that this scale discriminates between patients with different degrees of depression.[28] Consistent with this finding, the SDS patient group in the SIN-DEPRES study obtained lower scores on the SASS than non-SDS patients, not reaching social maladjustment. We believe that the scale is sensitive to a patient's change of status, reflects his/her perception, and is therefore a useful tool for evaluating response to treatment in this context.

### Predicting Recurrence

Different studies have shown that SDS in bipolar disorder are associated with an increased risk of recurrence.[13] The SIN-DEPRES study had an insufficient follow-up period to analyze this association, and recurrence rates were low. Other studies have reported a 24% recurrence rate after 6 months,[12] or 36% after 1 year in bipolar I disorder[44] and 61% after 2 years.[45] The NIMH Collaborative Depression Study, with 152 cases of bipolar I disorder, found recurrence rates of 48% and 57% after 1 year.[46] A study with a longer follow-up would provide a more precise determination on the relationship between SDS and risk of recurrence in ambulatory patients. In the STEP-BD study, the mean time to recurrence of any mood episode was 45 weeks (95% CI, 37.6–53.1).[12]

The present study has some limitations. The generalizability of our findings is limited to outpatients attending mental health centers. For instance, the fact that there was an overrepresentation of bipolar I patients over bipolar II may be explained by the fact that many bipolar II patients are attending primary care during depressive episodes, their hypomanic episodes going unnoticed. Another limitation is that, in our definition of prevalence, the duration that symptoms have been present is not considered. Finally, in future studies, clinical evaluations should not only address



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depressive symptoms but also be supplemented with evaluations of manic-hypomanic polarity symptoms. However, the SIN-DEPRES study is one of the largest prospective studies conducted in Europe aimed at assessing subthreshold depression. Our findings emphasize the importance of combining the clinician's and the patient's assessment. Clinicians may be sometimes less sensitive to mild depressive symptomatology, and variations in illness awareness may also make patient assessment more difficult.[47]

In conclusion, bipolar disorder is a chronic affective disorder largely dominated by minor or subclinical symptoms of depression (according to the definition) in bipolar I and II disorders. The SIN-DEPRES study highlights the frequency with which subclinical symptoms persist in ambulatory patients in whom the disorder is initially assessed as clinically stable.

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# Supplementary Material

**Article Title:** Detection of Subclinical Depression in Bipolar Disorder: A Cross-Sectional, 4-Month Prospective Follow-Up Study at Community Mental Health Services (SIN-DEPRES)

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## List of Supplementary Material for the article

1. eTable 1 Evolution of Depressive Symptoms According to Pharmacological Therapeutic Strategy

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**eTable 1**. Evolution of depressive symptoms according to pharmacological therapeutic strategy

| | | Clinical Stability for Depressive Symptoms[a] | | | Variation on MADRS Scale between Baseline and Final Assessments | | | |
|---|---|---|---|---|---|---|---|---|
| **Therapeutic strategy[b]** | ***n*** | ***n*** | ***%*** | ***CI 95%*** | **Mean** | ***SD*** | ***CI 95%*** | |
| Lithium | 88 | 82 | *93.2* | 85.9-96.8 | 0.2 | *3.6* | -0.61 | 0.93 |
| Anticonvulsivant agent | 90 | 78 | *86.7* | 86.7-92.2 | 0.7 | *5.9* | -0.54 | 1.91 |
| Lithium + Anticonvulsivant agent | 82 | 73 | *89.0* | 80.4-94.1 | 0.2 | *5.9* | -1.11 | 1.43 |
| Lithium + Antipsychotic agent | 98 | 86 | *87.8* | 79.8-92.9 | 0.0 | *5.2* | -1.04 | 1.04 |
| Lithium + Anticonvulsivant + Antipsychotic | 118 | 97 | *82.2* | 74.3-88.1 | 1.5 | *6.2* | 0.31 | 2.55 |
| Total[c] | 476 | | | | | | | |

CI, Confidence Interval

[a] Stability on depressive symptoms has been considered as being when a patient had not suffered considerable increases in the MADRS scale between study visits, defined as increases above 50% from the baseline score, and the score at the final visit in this scale was not higher than 7.

[b] The pharmacological therapeutic strategies defined are mutually excluding groups and all groups exclude the use of antidepressant agents.

[c] Other patients were under therapeutic strategies different from those defined for this analysis.

The studied BD patients were in maintenance therapy, registering a mean of 2.8 drugs per patient. Among the psychotropic agents prescribed, the most common were lithium carbonate (*n* = 442, 59.8%), followed by lamotrigine (*n* = 247, 33.4%), olanzapine (*n* = 176, 23.8%) and valproic acid (*n* = 146, 19.8%). Compliance with the maintenance therapy, according investigator's opinion, indicated that 83.6% of cases had good compliance (*n* = 618), while a 15% misses doses during a standard week (*n* = 111). A 70,1% of patients was satisfied with the maintenance treatment.