

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Not applicable

ACTIVE INGREDIENT: Not applicable

Study No: NIS-NES-DUM-2007/1 (NCT00690859)

Assessment of Predictive Factors for Bipolar Disorder Relapse in Spain (PREBIS)

Developmental phase: Not applicable

Study Completion Date: 10-07-2009

Date of Report: 8-06-2010

OBJECTIVES:

Main Objective

To study the factors relating to the occurrence of an acute episode affecting the subject's mood (depression, mania, hypomania or a mixed state) following a period of stabilisation in subjects with bipolar I or II disorder.

Secondary objectives

- To describe the clinical evolution of the disease in the cohort of subjects: duration of the inter-episode phase, clinical condition of the subjects between episodes, incidence of events regarding mood in the population and initial and predominant polarity.
- To describe the clinical and functional condition of the subjects during the different phases, with special attention paid to the assessment of sub-syndrome symptoms during stabilisation phases.
- To describe the consumption of health resources (hospitalisation, ambulatory resources, pharmacological treatments) according to the clinical condition of the subjects.

METHODS:

One-year epidemiological follow-up study of a cohort of patients complying with DSM-IV-TR criteria for bipolar I or II disorder.

Each patient will be assessed at the start and at months 3, 6, 9 and 12 after inclusion. Should there be additional visits required by the physician or the patient during follow-up, the reason for the visit and a basic set of data will be recorded during such visits.

Inclusion criteria

1. Subjects aged 18 and over.
2. Subjects agree to participate and sign the informed consent form.
3. Subjects comply with diagnostic criteria for bipolar I or II disorder according to DSM-IV-TR (Appendix I).
4. Treated at Mental Health Centres or ambulatory psychiatric clinics throughout the Spanish territory.
5. Subjects experiencing an episode of mood alteration (depression, mania, hypomania or mixed) within the last year and who are in partial or total remission for a minimum of 2 months.

Exclusion Criteria

1. Inability to carry out the follow-up plan, at the investigator's discretion.
2. Having participated in a clinical trial in the 6 months prior to the study.

Main variable

The main variable was the occurrence of relapses from the time the subject was considered to have recovered from a prior episode (two months without symptoms since the last acute episode, in order not to mistake it with a relapse of the previous episode) until the subject meets the criteria for a new episode, defined according to DSM-IV-TR.

Statistical analysis

χ^2 tests to compare discrete variables and bilateral t-tests to compare the mean values of continuous variables were used for the analysis of the main objective.

The main variable, the occurrence of an acute episode affecting mood (depression, mania, hypomania or mixed state) following a stabilisation period in patients with bipolar disorder, will be used to create a multivariate logistic regression model. All variables with a significance level of $p < 0.1$ in the univariate analysis will be used as predictive variables in the multivariate analysis.

The statistical significance of each predictive variable in the multivariate analysis will be verified using separate t-tests. Ratios and applicable range of 95% will be obtained to verify the influence of variables individually.

RESULTS:

609 patients diagnosed with bipolar disorder type I or II were initially recruited. 595 were finally included in the study and 593 were valid for the statistical analysis.

Table 1 Demographic and baseline characteristics

Demographics	
Age (years, SD)	47.25, 13.12
Sex, n (%)	237 male (40) 356 female (60)
Professional situation, n (%)	224 (37.8) employed
Educational degree, n (%)	104 (18) university 202 (34.9) high school 239 (41.3) primary school 34 (5.9) no studies

Primary objective

Factors associated with global recurrence:

- Last episode depressive (HR 0.39 [0.19-0.81], p 0.012).
- Number of hospitalizations (HR 8.19 [3.13-21.42]).

Factors associated with depressive recurrence:

- Treatment with antidepressants at V1 (HR 2.49 [1.21-5.14], p 0.014).

Factors associated with manic/hypomanic/mixed recurrences:

- Sex (female vs male) (HR 3.41 [1.15-10.13], p 0.027).
- Number of hospitalizations (HR 9.52 [2.61-34.77], p 0.001).

Secondary objectives

- *Clinical evolution of the disease*

Regarding the clinical characteristics of the sample, 501 patients (84.5%) had bipolar disorder type I and 92 (15.5%) had bipolar disorder type II. Basal scores of YMRS and MADRS are shown in tables 2 and 3.

Table 2: Basal YMRS score

V1	Male (N= 229)	Female (N= 337)	Total (N= 566)
BD I	3,54 (5,15)	2,63 (4,10)	3,00 (4,57)
BD II	2,68 (4,12)	2,36 (2,99)	2,48 (3,45)
TOTAL	3,42 (5,02)	2,59 (3,95)	2,93 (4,43)

Table 3: Basal MADRS score

V1	Male (N= 228)	Female (N= 339)	Total (N= 567)
BD I	5,06 (5,46)	5,57 (6,50)	5,36 (6,10)
BD II	6,06 (6,12)	7,16 (8,56)	6,73 (7,69)
TOTAL	5,20 (5,55)	5,81 (6,86)	5,56 (6,37)

The polarity of the first known episode and the predominant polarity are shown in table 4.

Table 4: polarity of the first known episode and the predominant polarity

N= 593	Male (N= 237)	Female (N= 356)	Total (N= 593)
POLARITY OF THE FIRST KNOWN EPISODE – N(%)			
DEPRESSION	97 (40,9)	192 (53,9)	289 (48,7)
MANIA	96 (40,5)	121 (34,0)	217 (36,6)
HYPOMANIA	35 (14,8)	21 (5,9)	56 (9,4)
MIXED	7 (3,0)	15 (4,2)	22 (3,7)
PREDOMINANT POLARITY – N(%)			
MANIC	26 (11,0)	34 (9,6)	60 (10,1)
DEPRESSIVE	16 (6,8)	16 (4,5)	32 (5,4)
NO PRED. POL.	195 (82,3)	306 (86,0)	501 (84,5)

31 (5.2%) patients had rapid cycling in the last year. 165 (27.9%) presented a seasonal pattern. There were 125 (21.1%) patients who had tried to kill themselves at any time.

Mean age when diagnostic of bipolar disorder was made was 35 years (SD 12.2). For type I the mean age was 33.8 years (SD 11.4) and for type II 41.7 (SD 14.0).

Mean number of episodes since the beginning of the disorder was 10.2 (SD 8.8) and mean number of hospitalizations was 2.8 being slightly higher among type I patients (mean 3.1) and lower among type II patients (mean 1.4).

The characteristics of the last acute episode by type are shown in table 5.

Table 5: polarity of the last acute episode

	Male		Female		Total
	I	II	I	II	
POLARITY OF THE LAST ACUTE EPISODE – N(%)					
MANIA	77 (13.4)	0	90 (15.7)	0	167 (29.1)
HYPOMANIA	47 (8.2)	12 (2.1)	43 (7.5)	14 (2.4)	116 (20.2)
DEPRESSION	61 (10.6)	21 (3.7)	124 (21.6)	43 (7.5)	249 (43.4)
MIXED	16 (2.8)	0	25 (4.3)	0	41 (7.1)
NO SPECIFIED	0	0	1 (0.2)	0	1 (0.2)
TOTAL	201 (35.0)	33 (5.7)	283 (49.3)	57 (9.9)	574 (100)

With regard to mood events during the study, 131 recurrences were recorded:

- 62 (47.3%) depressive.
- 57 (43.5%) manic.
- 8 (6.1%) mixed.
- 4 (3.0%) no specified.

- *Functional condition and sub-syndrome symptoms during the inter-episode phase*

Only 37.8% (224 patients) had a paid job, and 21.6% (128) were considered as disabled to work. The most impaired items of FAST score were work functioning, cognitive functioning and personal relationships, as shown in table 6.

Table 6: FAST scores

	V1	V2	V3	V4	V5
Autonomy	2,52	2,66	2,59	2,24	2,22
Work functioning	5,00	5,21	4,74	4,69	4,59
Cognitive function.	4,07	4,05	3,89	3,56	3,58
Finance	0,95	1,02	1,00	0,80	0,84
Personal relationships	4,10	4,14	4,10	3,73	3,70
Leisure	1,91	2,00	1,92	1,93	1,89
Total score	18,52	19,30	18,25	17,22	17,05

Regarding the presence of symptoms at inclusion, 72.7% (431 patients) were considered asymptomatic but 27.3% (162 patients) presented more than 2 symptoms (manic or depressive) despite not fulfilling criteria for mood episode and being in stable phase.

- *Consumption of health resources: pharmacological treatments*

Pharmacological treatments by therapeutic group were registered during the study (table 7).

Table 7: basal pharmacological treatment by therapeutic group

N= 593	V1
ANTIDEPRESSANTS	31,2
MOOD STABILIZERS	92,9
ANTIPSICHOTICS	56,3
BENZODIAZEPINES	38,4