AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA **PHARMACEUTICALS**

FINISHED PRODUCT: Not product related
ACTIVE INGREDIENT: Not product related

Study No: NIS-NEU-DUM-2009/1
Multinational ambispective study of the clinical management and burden of Bipolar Disorder (WAVE-bd Study)

Developmental phase: Post-marketing observational study
Study Completion Date: 07th June 2011
Date of Report: 16th May 2012

OBJECTIVES:

Primary objectives:

- To describe clinical management and clinical outcomes related to bipolar disorder (BD) in real-life settings in each of the participating country
- To evaluate the variability between countries and the factors associated with clinical outcomes (e.g. patient characteristics, country, treatment, adherence, etc.)

Secondary objectives:

- To estimate treatment adherence in BD and to identify patients at a higher risk of low adherence
- To assess quality of life (QoL) and functioning of BD patients in real-life settings
- To assess QoL and burden of BD patients' caregivers
- To calculate the use of health-care resources and to estimate the associated factors (e.g. low adherence to treatment, lack of disease control, etc.)
- To describe the population to whom quetiapine extended release (QTP XR) is prescribed and assess the factors related to this therapeutic strategy
- To assess differences in adherence to treatment, clinical outcomes, QoL, functioning, and use of health-care resources in BD patients receiving QTP XR versus other therapeutic practices in different countries

METHODS:

Study design

This was a multinational, multicenter, non-interventional, longitudinal study that aimed to identify medical needs associated with BD by providing reliable information on the management of BD patients in daily clinical practice in different countries. The study also aimed to determine factors influencing clinical outcomes and health-care resource use in relation to the management of BD.
The study included 2 phases:

1. A retrospective phase which was the period from the patient's index event (the first episode/mood event in the retrospective phase) to the date the patient signed the informed consent form (ICF).
2. A prospective phase which was the period from the date of signing the ICF to the last visit of the last patient included in the study.

Target population and sample size

Patients enrolled in the study had bipolar disorder I (BD-I) or bipolar disorder II (BD-II) and experienced at least one mood event during the 12 months before the beginning of the study. In order to obtain a heterogeneous study population reflective of the real-life clinical practice of each of participating country, patients were recruited from various types of health centers (mental health centers, clinics, private settings, hospitals, or specialized units). Patients' caregivers were also involved in the study.
A total number of 2965 patients from 221 centers satisfied the inclusion/exclusion criteria and were enrolled in the study, and 2896 patients were included in the final analysis.

Criteria for evaluation

Patients' demographics, medical history, disease characteristics, treatment information were collected. Clinical outcomes were assessed by an electronic adaptation of the National Institute of Mental Health-Life Chart Methodology (NIMH-LCM^{TM}) and by the Clinical Global Impression for Bipolar Illness scale. Treatment compliance was assessed using a 10-item version of the self-applied scale DAI and the MPR. Patients' QoL and functioning were evaluated using the EuroQoL-5D (EQ5D) and the Functioning Assessment Short Test (FAST). Health-care resource consumption was assessed by evaluating the number of scheduled and non-scheduled visits, the number of emergency room and primary care visits, the number and length of hospitalizations due to BD, the number of tests performed (for diagnosis, monitoring, or other reasons), and the number of other outpatient facilities visited. Caregivers' demographics were collected as well, and their burden was evaluated using the Burden Assessment Scale (BAS). Methods for collecting patient reported outcomes (PROs) comprised the EQ5D and the PRO questionnaires. Since this was not an interventional study, adverse drug reactions were not collected unless they were spontaneously reported by patients.

Statistical Methods

A descriptive analysis approach was used for continuous and categorical variables. A two-sided 95% confidence interval (CI) was applied for the population estimation of the variables.

For study outcomes that were dichotomous variables, mixed model logistic regression for the analysis of the determinants of the study outcomes were used. To estimate the association between time to recurrence/relapse/suicide attempt with individual participant characteristics Cox Proportional Hazard models stratifying by center were used. To estimate the association of number of relapse/recurrence/suicide attempts with individual participant's characteristics Poisson Regression models stratifying by center were used. For study outcomes that were continuous variables, random-intercept mixed linear regression models were used.

In order to assess differences in adherence to treatment, clinical outcomes, quality of life, functioning and use of health-care resources in patients receiving QTP XR versus other therapeutic practices (any other medication, any other atypical antipsychotic and quetiapine immediate release [QTP IR]) a first step was to calculate the propensity score to compare patient profiles between treatment groups. To see whether the patient profiles in the groups are comparable, distribution of propensity score for the QTP XR patients should be within the range of the distribution of propensity score for the other treatment group patients. For calculating the propensity score, a logistic regression was used taking the variable QTP XR/other treatment group as dependent variable and all the demographic and baseline characteristics and study index episode characteristics recorded in the eCRF as independent variables. In order to assess factors associated to the prescription of QTP XR vs. other therapeutic practices, multivariate logistic regressions were done with the variable QTP XR/other therapeutic practice as dependent variable and site characteristics, demographics, medical history, disease characteristics and study index episode characteristics as independent variables.

RESULTS:

Patient demography and social characteristics

A total of 2896 patients with mean age of 46.7 years were included in the final study analysis, the majority of whom were female (62.0%) and white (91.2%).
Social and demographic characteristics were mostly similar across all 10 countries involved in the study. A total of 362 patients (12.5%) were classed as alcohol or drug users in the study. This proportion varied between countries, from 2.2% in Turkey to 25.6% in France.

Around half of all patients (49.0%) suffered from co-morbidities or had relevant history of a medical condition that required chronic drug therapy or invasive surgical treatment. This percentage was similar for most countries and ranged from 66.7% of patients in Romania to 34.4% of patients in Turkey.

Demographic and social characteristics were similar between patients with BD-I and BD-II.

Patient baseline disease characteristics

The mean age that a patient was diagnosed with BD was 34.9 years, ranging from 27.4 years in Turkey to 40.6 years in Romania. A total of 39.5% of patients had psychotic symptoms at diagnosis (ranging from 30.2% in France to 52.0 % in Venezuela). Mean patient age for age of diagnosis for both BD-I and BD-II was similar. The percentage of patients with psychotic symptoms at diagnosis was higher in patients with BD-I (50.3%) and substantially lower in patients with BD-II (7.2%).

The mean time from diagnosis to index event for the total population was 10.5 years, and this was similar for all countries and for patients with both BD-I and BD-II. A total of 67.1% of the study population had been hospitalized due to BD during the period from diagnosis to index event, and 20.6% had attempted suicide. Hospitalization and suicide rates were similar between countries, except for Ukraine, where only 8.6% of patients attempted suicide during this time. More patients with BD-I were hospitalized and attempted suicide compared to patients with BD-II.

The majority of patient index events were depressive (53.4%), followed by manic (22.0%) and hypomanic (16.5%). Depression was the most common index event for all countries except for Turkey, where it was mania (47.4%). A depressive index event was much more common in patients with BD-II (77.7%) compared to BD-I (42.3%).

Patient clinical outcomes

A total of 18.2% of patients had a reported disease relapse during the study. The incidence of reported relapse was similar for all countries, except for Turkey (6.2%) and Austria (34.4%). The most common type of reported relapse was depressive (11.4%), followed by hypomanic (5.9%). Depressive relapse was also the most common type of reported relapse for both BD-I and BD-II patients. Patients were numerically more likely to have a reported relapse (of any polarity, with a mean incidence rate ratio [IRR] >1.05) when they were treated in primary care (incidence rate ratio [IRR] 2.86 [95% CI 2.05; 3.99]), had attempted suicide between diagnosis and the study index event (IRR 1.97 [95% CI 1.63; 2.39]), had rapid cycling (IRR 1.86 [95% CI 1.54; 2.25]), had any familial mental illness (IRR 1.85 [95% CI 1.50; 2.30]), were 65 years old or older (IRR 1.51 [95% CI 1.05; 2.19]), lived alone (IRR 1.31 [95% CI 1.07; 1.61]), or were treated with antidepressants at their study index event (IRR 1.39 [95% CI 1.12; 1.71]). Patients were numerically less likely to have reported relapses of any polarity (with a mean IRR <0.95) when they were treated in a mental health center (IRR 0.27 [95% CI 0.16; 0.46]). Patients had a numerically shorter time to their first reported relapse (with a mean HR >1.05) when they had rapid cycling (HR 2.15 [95% CI 1.50; 3.06]), had attempted suicide between diagnosis and the study index event (HR 2.06 [95% CI 1.44; 2.95]), were treated in primary care (HR 1.90 [95% CI 1.07; 3.36]), or were treated with anticonvulsants at the study index event (HR 1.46 [95% CI 1.02; 2.09]). No factors seemed to be associated (with a mean HR <0.95) with a longer time to first reported relapse.

A total of 40.5% of patients had a reported recurrence during the study. The incidence of recurrence ranged from 20.1% in Turkey to 63.2% in Austria. The most common type of recurrence was depressive (23.1%), followed by hypomanic (10.1%). Depressive recurrence was the most common type of recurrence for both BD-I (19.4%) and BD-II (31.3%). Patients were numerically more likely to have reported recurrences of any polarity (with a mean IRR >1.05) when they were an alcohol or drug abuser (IRR 1.62 [95% CI 1.32; 2.00]), had any familial mental illness (IRR 1.29 [95% CI 1.10; 1.51]), had rapid cycling (IRR 1.37 [95% CI 1.14; 1.64]), or were treated with anxiolytics, sedatives or hypnotics at their study index event (IRR 1.21 [95% CI 1.03; 1.44]). No factors seemed to be associated with IRR (with a mean IRR <0.95) of reported recurrences of any polarity. Patients had a numerically shorter time to their first reported recurrence (with a mean HR >1.05) when they were alcohol or drug abusers (HR 1.64 [95% CI 1.26; 2.12]), were treated in private practice (HR 1.46 [95% CI 1.10; 1.93]), had rapid cycling (HR 1.37 [95% CI 1.08; 1.73]), or a seasonal pattern of BD (HR 1.26 [95% CI 1.02; 1.55]). No factors seemed to be associated (with a mean HR <0.95) with a longer time to first reported recurrence.

A total of 3.4% of patients attempted suicide during the study. Incidence of suicide attempt was lowest in Turkey (0.8%) and Ukraine (1.8%), and was highest in France (5.6%) and Belgium (5.2%). Patients were numerically more likely to attempt suicide (with a mean IRR >1.05) when they had already attempted suicide between diagnosis and the study index event (IRR 13.87 [95% CI 7.00; 27.49]), or had been treated with antidepressants at the study index event (IRR 1.97 [95% CI 1.09; 3.57]). No factors seemed to be associated (with a mean IRR <0.95) with patients who were numerically less likely to attempt suicide. Patients had a shorter time to their first suicide attempt during the study (with a mean HR >1.05) if they had already attempted suicide between their diagnosis and study index event (HR 14.27 [95% CI 7.02; 29.02], p<0.001). No factors were associated with a longer time (with a mean HR <0.95) to first suicide attempt.

Patient clinical management

Out of the patients who had an episode, the percentage of these patients who were receiving treatment was consistent whether the episode polarity was manic, hypomanic, depressive, or mixed, and ranged from 89.0% (manic episode) to 93.7% (mixed episode). The percentage of patients who received treatment was also comparable between countries, although Turkey consistently had the lowest percentage of patients who received treatment for an episode of any polarity. Out of the patients who had an episode, the percentage of these patients who received treatment was comparable between BD-I and BD-II.

Atypical antipsychotics were the most common specific treatment in patients with manic, hypomanic, depressive, or mixed episodes (57.2% of patients in depressive episodes to 77.6% of patients in manic episodes). Treatments were generally similar between countries, although it is of note that the number of patients during manic episodes who were being treated with lithium was exceptionally low in Romania (3.4%). The proportion of patients treated with lithium tended to be exceptionally high in Brazil, for example lithium was the most common treatment in Brazilian patients with mania (58.3%).

Treatments were mostly comparable between BD-I and BD-II, and atypical antipsychotics were the most common treatment for both BD types in both hypomanic and depressive disease phases. However in hypomanic episodes atypical antipsychotics, lithium, and typical antipsychotics were more common in patients with BD-I (≥ 5% difference). Lamotrigine, selective serotonin-reuptake inhibitors (SSRIs), and selective norepinephrine-reuptake inhibitors (SNRIs) were more common in patients with BD-II (≥ 5% difference). In depressive episodes atypical antipsychotics, lithium, and valproic acid were more common in patients with BD-I (≥ 5% difference), and lamotrigine and SNRIs were more common in patients with BD-II (≥ 5% difference).

A total of 93.9% of patients who were in euthymia during the study were receiving treatment and this percentage was comparable in all countries, ranging from 85.6% in Turkey to 99.6% in Venezuela. The percentage of patients who were receiving treatment during euthymia was also comparable between BD-I and BD-II.

Atypical antipsychotics were the most common specific treatment in patients during euthymia, followed by valproic acid and lithium. Atypical antipsychotics were the most common specific treatment in patients during euthymia in all countries except for Brazil, where it was lithium. Treatments in patients during euthymia were mostly comparable between BD-I and BD-II, and atypical antipsychotics were the most common treatment for both BD types in euthymia. However lithium, atypical antipsychotics and typical antipsychotics were more common in patients with BD-I (≤ 5% difference), and lamotrigine, heterocyclic antidepressants, and SNRIs were more common in patients with BD-II (≤ 5% difference).

Patients during euthymia had a mean (± standard deviation [SD]) number of 2.89 (±1.43) treatments; patients during mania had a mean (±SD) number of 2.84 (±1.49) treatments; patients during hypomania had a mean (±SD) number of 2.61 (±1.32) treatments; patients during depression had a mean (±SD) number of 3.11 (±1.53) treatments; patients during mixed episodes had a mean (±SD) number of 3.17 (±1.53) treatments. The number of treatments was similar between countries and BD type, although BD-I patients tended to have a slightly higher number of treatments.

Patient treatment adherence

Treatment adherence was generally high for patients in episodes of all polarities, and the overall percentage of patients with low adherence was small. Treatment adherence was highest in patients who had a mixed episode (96.8%) and lowest in patients who had a depressive episode (88.1%). Treatment adherence varied between countries. France had the highest proportion of patients with low treatment adherence during manic episodes, and Germany had the highest proportion of patients with low treatment adherence during hypomanic, depressive, and euthymic episodes. Treatment adherence between BD-I and BD-II was similar. Only patients who were treated in hospital were more likely to have non-treatment adherence in euthymia, however patients who were more likely to have non-treatment adherence in depression were treated in private practice, or were alcohol or drug abusers.

Patient quality of life and functioning characteristics

QoL in study patients varied between disease phases, country, and type of EQ5D scale used (EQ5D-index or EQ5D-visual analogue scale [VAS]). Interestingly, patients during euthymia had the lowest mean (±SD) EQ5D-index (0.41±0.27), and patients during hypomanic episodes had the highest mean (±SD) EQ5D-index (0.69±0.28). Patients during hypomania also had the highest E5QD-VAS score of 71.9±18.4, and patients with depressive episodes had the lowest E5QD-VAS score (53.0±21.2). Brazilian patients rated lowest on the EQ5D index compared to other countries for all polarities except for euthymic patients. Turkish patients rated highest on the EQ5D index compared to other countries for all polarities except for hypomanic patients. No trends were noted between countries for E5QD-VAS scores. Both EQ5D-index and E5QD-VAS scores were similar between patients with BD-I and BD-II.

Patients who were treated with lithium at the index event had a slightly higher EQ5D-index. Patients who had a longer period of euthymia since diagnosis had a slightly higher EQ5D-VAS score. Patients who had a lower EQ5D-VAS score had anxiety disorder, were over 65 years old, had attempted suicide between diagnosis and the study index event, had a higher number of hospitalizations due to BD since diagnosis, had a higher age for first symptoms compatible with disease, and were treated with antidepressants at the study index event.

Patient functioning was generally similar between countries and BD type, as judged by FAST scoring at the study inclusion visit. Total patient mean (±SD) FAST score was 49.64 (±17.00), ranging from 43.99 (±14.59) in Ukraine to 54.26 (±16.60) in Belgium. FAST domain scores were also similar between countries and BD type. Mean (±SD) FAST autonomy score was 7.50 (±3.24), mean (±SD) FAST occupational functioning score was 11.63 (±5.02), mean (±SD) FAST cognitive functioning score was 10.58 (±4.09), mean (±SD) FAST interpersonal relationships functioning score was 12.05 (±4.66), mean (±SD) FAST leisure time score was 4.48 (±1.97), and mean (±SD) FAST financial issues score was 3.77 (±1.94).

Patients who tended to have higher FAST total score (and therefore had lower functioning ability) were over 65 years of age, were treated with antipsychotics at the index event, had psychotic symptoms at the study index event, had rapid cycling, had anxiety disorder, had a somatic condition, had attempted suicide between diagnosis and the index event, had a longer time between diagnosis and the index event, had a higher number of hospitalizations since diagnosis, or had a higher age for first symptoms compatible with disease.

Patients who had a lower FAST score (and therefore had higher functioning ability) had a higher number of visits to group therapy from index event to inclusion visit, or had a longer period of euthymia since diagnosis.

Patient health care resource utilization

The incidence rate (incidence rate per person per year) of total health care resources use was 11.17 per patient per year. Patient use of health care resources was similar between countries, and ranged from an incidence rate of 7.62 in Portugal to 19.12 in Austria. Programmed visits to psychiatrists were the biggest single health care resource used by patients in all countries, ranging from an incidence rate of 5.04 in Ukraine to 9.42 in Romania. In general, patients in Romania, Austria, and Germany used health care resources the most frequently, and patients in Brazil, Venezuela, Turkey, Portugal and Ukraine used health care resources the least frequently. Patients with BD-I had slightly higher incidence rate for using health care resources.

Patients had a higher total number of visits per year if they had rapid cycling, thyroid disease, were treated with antipsychotics at the index event, or had a higher number of hospitalizations since diagnosis. Patients had a lower incidence of total visits per year if they were treated in a mental health center.

Patient caregiver burden

Demography and social characteristics of patient caregivers were similar by country and BD type. Mean (±SD) BAS total score for caregivers was 44.6 (±13.3), ranging from 36.1 (±9.6) in Germany to 61.3 (±7.6) in Austria. Caregivers had higher BAS scores if their patients were an alcohol or drug abuser, if they had psychotic symptoms at their index event, or if their patient had a higher number of hospitalizations since diagnosis.

Analyses of quetiapine extended-release treated population in WAVE-bd study

A total of 10.9% of the study population were taking QTP XR at their index event, ranging from 0.6% in Ukraine to 30.1% in Portugal. The proportion of patients who received QTP XR at mental health centers was lower than for other treatments, including QTP IR (4.4% QTP XR versus 8.1% QTP IR), however the proportion of patients treated with QTP XR in primary care was higher than for other treatments , including QTP IR (14.2% QTP XR versus 5.6% QTP IR).

The demography of patients treated with QTP XR was similar to patients treated with other therapies in some ways, however a higher proportion of patients treated with QTP XR had a psychiatric disorder (21.6%), or a family history of psychiatric disorder (69.4%), and the percentage of patients treated with QTP XR who had a hypomanic (14.9%) or mixed (6.0%) event at diagnosis was slightly higher than for patients treated with other therapies. The duration of patient study index events was similar for all therapies in patients with manic, hypomanic, and depressive index events; however the duration of mixed index events was longer for QTP IR compared to QTP XR and other therapies. The mean (±SD) longest period of euthymia since diagnosis was slightly shorter for patients treated with QTP XR compared to patients treated with other therapies. Patients treated with QTP XR also had a higher incidence rate of hospitalization between diagnosis and their index event compared to patients treated with other therapies.

Patients were numerically more likely to be treated with QTP XR compared to any other treatment (except QTP IR) if they were in primary care, were under 65 years old, had co-morbidity of obesity, had a family history of BD, had previously been hospitalized due to BD, or had psychotic symptoms at their index event. Patients were numerically more likely to be treated with QTP XR compared to any other atypical antipsychotic (except QTP IR) if they were under 65 years old, in primary care, had co-morbidity of obesity, or a family history of BD. Patients were numerically more likely to be treated with QTP XR compared to QTP IR if they were in primary care, were on disability pension, had a family history of BD, had polarity of mania, hypomania, or mixed at diagnosis, had co-morbidity of obesity, or psychotic symptoms at their index event. Patients were numerically less likely to be treated with QTP XR if they had a co-morbidity of dyslipidemia.

Propensity score distributions were different between patient treatment groups. Only around half of patients in each treatment group (other therapies, other atypical antipsychotics, or QTP IR) had similar characteristics compared to patients prescribed QTP XR. As propensity score distributions were different between treatments, direct comparisons between treatment groups regarding clinical outcomes, treatment adherence, QoL, patient functioning and use of resources were not compared.
Additional studies are needed in order to further differentiate QTP XR and QTP IR prescription.