NIS REPORT SYNOPSIS

NIS Name/Code NIS-NBE-SER-2008/1

HARMONY: A 6 month observational multicentric prospective study observing the use of atypical antipsychotics in patients diagnosed with Bipolar I or II Disorder, in the course of a major depressive episode.

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Objectives

- The primary objective was to observe the parameters of use (dosage, reason of use, treatment starting date) of AAPs in Bipolar I or II Disorder in the course of a major depressive episode.

The secondary objectives were to observe

- the remission rate for the major depressive episode in progress at inclusion in the study through evaluation scales (the Montgomery Asberg Depression Rating Scale [MADRS] and the Young Mania Rating Scale [YMRS].
- the percentage of recurrence of a depressive, hypomanic, manic or mixed episode
- the quality of life of the patient through a patient-reported questionnaire (the Quality of Life Enjoyment and Satisfaction Questionnaire Short Form [Q-Les-Q SF])
- the evolution of the severity of the patient's pathology through the Clinical Global Impressions scale for use in Bipolar illness [CGI-BP])

and

- to investigate any potential factors that may influence the treatment choice.

Method

This NIS was a multicentre, prospective study. Patients diagnosed with Bipolar I or II Disorder, in the course of a major depressive episode (according to the DSM-IV-TR) were enrolled in the study at 37 sites across Belgium. The study was designed to observe the parameters of use (dosage – reason of use – treatment starting date) of AAPs in the patient population at 4 visits over 6 months. Demographics, psychiatric history and current AAP treatment, other psychotic medication and baseline observations were assessed at Visit 1. During the next 3 visits (V2, V3, V4), any changes in AAP or psychotropic medication, any psychiatric hospitalisations, substance abuse, recurrence of a mood event and effect on work/school treatment were assessed and compliance of AAP(s) was recorded. In addition, the patient's clinical condition was assessed by the psychiatrist at each visit using the MADRS,

YMRS and CGI-BP observer rating scales and by the patient using the self-administered questionnaire Q-Les-Q SF.

Number of patients:152

Main criteria for inclusion

- Willing and able to provide written informed consent
- Male or female ≥ 18 and ≤ 65 years of age, able to read and write
- Outpatients, diagnosed with Bipolar I or II Disorder, having presented or presenting with a major depressive episode (according to DSM-IV-TR) with a starting date of 6 months maximum before the inclusion.
- Current treatment with atypical antipsychotic(s) (AAP(s)) minimal 1 month and maximum 6 months prior to the first study visit
- Patient taking an AAP at an adequate therapeutic dose as indicated in the local Summary of Product Characteristics (SPC) and current medical practice
- Able to understand and comply with the study requirements

Study Drug, Dose and Mode of Administration

Atypical antipsychotics were used according the SPC and the current medical practice. Additional psychotropic medication was recorded at each visit.

Duration of Treatment

The patients were followed for a maximum of 6 months.

Criteria for Evaluation

The primary variable was the details of any AAP prescribed 1 to 6 months prior to the first study visit. The name, dose, starting date, monotherapy or combination therapy and indication, was documented.

The secondary variables were the Montgomery Asberg Depression Rating Scale (MADRS), Young Mania Rating Scale (YMRS), remission rate for the major depressive episode, recurrence rate, Quality of life enjoyment and satisfaction questionnaire, short form (Q-Les-Q SF), Clinical Global Impressions scale for use in Bipolar illness (CGI-BP), diagnosis and age of onset, hospitalisation, history of AAP treatment, number of mood episodes, concomitant psychotropic medication, comorbidities, substance use, treatment compliance and the impact on work/school.

Criteria for Evaluation – Safety

No safety details were collected in this study

Statistical Methods

The primary variable, use of APPS, was analysed with descriptive statistics.

Continuous data is described by their mean, standard deviation, median, lower and upper quartile, minimum and maximum and valid cases. Categorical data is described by absolute and percentage number of subjects per category.

All tests were performed two-sided at a 5% level of significance. No adjustment for multiple testing was done. Two-sided confidence intervals are displayed for important variables.

The AAPs and concomitant medications were coded according to the WHO-Drug Dictionary

Depression was assessed using the Montgomery Asberg Depression Rating Scale (MADRS). Scoring was based on a flexible interview on a six-point rating scale. The rater had to decide between the defined scale steps (0-2-4-6) or choose in-between values (1-3-5). Ten items were available, representing one symptom each, the total score was calculated by summation.

Manic symptoms were assessed using the Young Mania Scale (YMRS). The scale has 11 items and is based on the patient's report of his or her clinical condition over the previous 48 hours, done by a clinician or trained rater.

The severity of illness and improvement were assessed using the Clinical Global Impression (CGI).

The quality of life (degree of enjoyment and satisfaction) was assessed by means of the Short Form of the Q-LES-Q.

Each of the questionnaires was analyzed by visit. Changes from baseline were calculated and compared between visits using descriptive statistics.

RESULTS

The majority of patients enrolled in the study were being treated with combined therapy with other psychotic medications, mainly anti-epileptica and anxiolytics, sedatives or hypnotics. Fourteen patients (9.2%) were being treated with antipsychotic monotherapy.

At the time of enrolment 42.7% of patients (64/150) in the safety dataset were prescribed quetiapine for depressive symptoms and 7 patients were prescribed it for other reasons. The mean dose of quetiapine was 229.8 mg /day, range 10mg to 600mg plus one outlier of 900mg/day.

"Other antipsychotics" (olanzapine, aripiprazole, risperidone or paliperidone) were being taken by 40.0 % of patients (60/150), three patients were taking amisulpride and one patient chlordiazeoxide for depressive symptoms, and 17 (11.3%) for other reasons. All except 4 patients had been taking the current antipsychotic for $\leq$ 6 months. The mean dose of olanzapine was 9.3 mg/day (range 5 to 30 mg), for aripiprazole 12.7 mg (range 1 to 30 mg); for risperidone 1.8 mg (range 1 to 6 mg); for paliperidone 3.9 mg (range 3 to 6 mg).

Overall antipsychotics were being taken by 127 patients for a depressive episode and by 23 patients for manic or other illnesses. No indication for treatment with antipsychotics was

given for 2 patients.

Psychiatric co-morbidities were reported for 39.3% of the patients and 5.3% had other co-morbidities that were not specified. The most frequent psychiatric co-morbidity was anxiety disorder in 33.3% of patients (50/150).

Significantly more males than females were prescribed quetiapine for depressive symptoms (52.6% to 36.2% respectively; p= 0.047, Chi square test). For the other antipsychotics more females (42.6%) than males (35.1%) were prescribed antipsychotics. Patients who first developed symptoms at a younger age (≤30 years) were prescribed quetiapine less frequently than patients who developed symptoms when older (27 patients to 37 patients, p=0.017 Chi-square test). For other antipsychotics there was no significant difference between groups for age of onset of first symptoms.

No significant difference was seen between patients who had had previous AAP treatment and treatment naive patients in the choice of current treatment with AAP and no significant difference in the treatments between patients at work and patients not in a work /school situation was seen.

Substance abuse was reported in 69 patients at Visit 1, but there was no significant difference in treatment selection in patients who were known to be abusing drugs compared to patients with no substance abuse.

During the 6 months of observation, the number of patients treated with AAPs for depressive symptoms decreased over time. At Visit 1 there were 64 patients taking quetiapine and 60 taking other antipsychotics and at Visit 4 the numbers had decreased to 18 patients taking quetiapine and 12 taking other antipsychotics in the ITT dataset.

During the study the overall bipolar illness improved and at the end of the study 70.5% of patients (79 patients) were much or very much improved compared to their worst phase of the illness. At the end of the study 27.7% of patients (31 patients) were not ill according to the investigator, 29.5% were minimally ill, 37.5% were mildly, moderately or markedly ill and six patients (5.4%) were severely ill. There was also a gradually increase in the number of patients who were in remission for the depressive episode and by the end of the study, 61.3% of the patients who completed the study were in remission. The improvement in patients was also reflected in the improvement in their quality of life as assessed by the patients, the mean score increased from 52.3 at Visit 1 to 60.6 at Visit 4, with a significant mean change to baseline of 8.3 ($p < 0.001$, paired t-test).

The Montgomery Asberg Depression Rating Scale and Young Mania Rating Scale also improved during the study; mean overall MADRS decreased from 20.9 at Visit 1 to 11.1 at Visit 4, mean change to baseline of -10 points ($p < 0.001$, paired t-test). The mean score on the YMRS scale decreased from 3.3 at Visit 1 to 2.5 at Visit 4 with a mean change from baseline of -0.8 ($p = 0.04$, paired t-test).