SYNOPSIS

Name of Sponsor/Company: Name of Finished Product: Name of Active Ingredient(s):	Janssen-Cilag, S.A. Risperidone Risperidone

Protocol No.: CR005755
Title of the study: A Mental Health Registry called: ADH.E.R.E.: Treatment Adherence and Strategies: A Mental Illness Registry

Coordinating Investigator(s): Fernando Cañas Rodríguez, M.D. (Hospital Lafora , Madrid) and José Ramón Gutiérrez Casares (Hospital Infanta Cristina, Badajoz).

Publication (Reference): None

Study Initiation/Completion Dates: June 2005 – March 2006 | **Phase of Development:** Non applicable

Objectives: The purpose of this non interventional study was to evaluate the degree of treatment compliance over the first few months after implementing a new therapeutic strategy (i.e. psychotherapy sessions, patient's interview in Day Care clinics, pharmacologic interventions, etc) for patients with schizophrenia during ambulatory follow-up.
Secondary objectives of the study were:
1. To compare the level of treatment adherence and compliance of schizophrenic patients vs. those with other severe and chronic mental disorders such as bipolar disorder, personality disorder, and depression in ambulatory patients.
2. To evaluate the methods used by psychiatrists to examine treatment adherence in routine clinical practice

Methodology: This was a six-month, multi-centre, retrospective-prospective, epidemiological, open design study for retrieving information related to the 3-month period previous to entering the registry file and follow-up data 3 months later, of consecutive ambulatory patients who visit the psychiatrist' office with a diagnosis of schizophrenia (S), bipolar disorder (BD), personality disorder (PD), or depression (D), according to DSM-IV criteria (codes 295.10, 295.20, 295.30, 295.40, 295.60, 295.70, 295.90; 296.XX, 301.XX).
This registry was done within the usual conditions of clinical practice without restrictions to the participant investigators prescribing what they consider the most appropriate treatment at each moment.

Number of Subjects (planned and analyzed): Based on the incidence described in the medical literature and the number of participant investigators, a plan was done to retrieve information on 2526 consenting patients satisfying the inclusion criteria from 300 selected investigators in Spain.
During the inclusion period, each participant investigator enrolled the first patients attending his or her office who comply with all the inclusion criteria, none of the exclusion criteria, sign the informed consent form and the following diagnostic criteria: First 7 schizophrenic patients; first patient with personality disorder; first patient with a diagnosis of depression; and first patient with bipolar disorder.
Finally, a total of 2622 patients were eligible to participate and analyzed from 286 investigators.

Diagnosis and Main Criteria for Inclusion: Ambulatory males and females with schizophrenia, bipolar disorder, personality disorder, or depression, according to DSM-IV criteria (codes 295.10, 295.20, 295.30, 295.40, 295.60, 295.70, 295.90, 296.XX, 301.XX) in which a new therapeutic intervention is started (psychotherapy, pharmacological treatments, other non-pharmacological measures, etc) lasting for at least 3 months since the date of change, and a minimum of 3 months follow-up. Patients' ambulatory follow-up done in the investigator's centre to allow him or her full access to previous clinical data on patient's treatment strategies for the past 3 months.

Test Product, Dose and Mode of Administration, Batch No.: Non applicable. This was an observational epidemiological study carried out according to the general clinical practice. Therefore, no intervention was performed on pharmacological and non-pharmacological treatments.

Reference Therapy, Dose and Mode of Administration, Batch No.: Non applicable.

Duration of Treatment: Non applicable.

SYNOPSIS (CONTINUED)

Criteria for Evaluation: The primary endpoint for this study was to evaluate the patients' adherence to treatment strategies at baseline (when the new pharmacological or non-pharmacological strategy is started) and after the 3-months follow-up period:

a) Adherence to non-pharmacological treatments by follow-up clinical evaluation, follow-up by nurse, and other assessments (psychotherapy, etc.) while attending the psychiatric unit, nurse unit, rehabilitation unit and/or day care centre.

b) Adherence to pharmacological treatments by evaluating the type of treatment: antipsychotic drugs, mood stabilizers, or antidepressant drugs. Compliance for outcome and for methods of treatment were measured by direct questions to patients, close relatives/caregivers or other relatives/caregivers; evaluation scales; drug/injections accountability; and Medication Event Monitoring System (MEMS).

Safety: The assessment of safety was based on recording adverse events detected during the follow-up period.

Statistical Methods: Continuous variables are described by presenting the following summary statistics: number of patients with non-missing values (n), mean, standard deviation (SD), median, minimum and maximum. Categorical variables were summarized by presenting the number of patients, the percentage for each category and the corresponding confidence interval of 95% (CI 95%). A statistical significance level of 0,05 was considered for all statistical tests. Statistical analysis was done with SAS v9.1.

The statistical analysis includes a description of the study population with retrospective, baseline, and prospective data; an analysis to establish possible associations within study variables; and a safety analysis of adverse events recorded.

Assessment of patients' adherence to treatment was based on the following variables: diagnosis, insight, substance abuse, Clinical Global Impression scale (CGI), and socio-demographic data.

A multivariate analysis was done to evaluate the possible influence of the schizophrenia diagnosis as a predictive factor on patients' adherence to treatment, together with other covariates that may influence the model: patient's sociodemographic characteristics, other diagnosis, baseline characteristics, or different therapeutic strategies. All different diagnosis were analyzed individually.

Association of qualitative variables were evaluated by the Chi-square test or the exact Fisher test, when appropriate.

Explanatory variables of treatment adherence did not follow a normal distribution model and thus, analysis regarding their possible association with all other study variables was performed by the Kruskall-Wallis non-parametric test.

Pearson's correlation coefficient was calculated to detect a possible association of quantitative variables with the above mentioned treatment adherence variables.

SUMMARY – CONCLUSIONS

Main objective: Concerning *adherence to non-pharmacological treatments*, the percentage of patients showing adherence >80% was lower in the PD group that in the other pathologies, both at baseline and follow-up visit, for all the non-pharmacological interventions evaluated. Concretely, when S group was statistically compared to the rest of pathologies, a statistical difference was observed between S and PD for the interventions "Follow-up visit" and "Other non-pharmacological interventions" at baseline visit, and for "Follow-up visit" and "Follow-up visit with nurse" in the 3-month visit. Overall, when the % of patients with adherence > 80% was compared between baseline and 3-month visit, a statistical significant increase was observed in both "Follow-up visit" and "Follow-up visit with nurse", from 74-79% at baseline to 89%.

When evaluating *pharmacological treatment*, 70% of patients with S were treated with atypical antipsychotics (83% oral) at baseline while 24.5% were receiving conventional antipsychotics (62% oral). Only 51.6% of them admitted a level >80% of adherence to pharmacological treatment when directly asked (34.9% when the questions were answered by a close relative/caregiver). This percentage was significantly lower when patients with PD were asked about their compliance, and even lower when some relative was asked. In contrast, the percentage of patients with BD or D assuring compliance >80% was significantly higher than in S group. When compliance was evaluated through scales, the percentage of patients with S showing compliance rates >80% was lower than 37%. And when pharmacological adherence was evaluated through MEMS, only 28.9% of schizophrenic patients showed >80% of dosage accomplishment; this figure was higher in the rest of the studied pathologies, although differences only reached statistical significance when compared with BD or D (compliance >80% as measured with MEMS: D>BD>PD>E). In contrast to these poor compliance rates, when adherence to pharmacological treatment was evaluated through injections accountability, 79% of patients with S showed rates >80%. In summary, for schizophrenic patients, compliance degrees >80% showed statistically significant differences depending on the evaluation method (max. 79% for injections; min. 29.8% when measured by MEMS; 45% by questions). A multivariate analysis of the schizophrenic patients population showed that significant explanatory variables for both non-pharmacological and pharmacological compliance at baseline are the number of previous hospitalizations, degree of family support, substance abuse, and insight.

In the group of patients with S, 66,3% had a change in pharmacological therapy at baseline, 6% in non-pharmacological therapy and 15.6% had a change in both strategies. At the follow-up visit, 79,8% of patients with S were treated with atypical antipsychotics (70% of them with long-acting injectable formulation), and 85% of them admitted a degree of compliance >80% to pharmacological treatment (a similar 83% when the questions were answered by a close relative/caregiver). Compliance rates in S patients were similar when measured by questions, MEMS, scales, pill accountability, and a little higher with injection accountability. When comparing S with the other pathologies, differences were only found with patients PD, who showed lower levels of compliance than the rest.

In general, compliance to pharmacological treatment was higher at the 3-month follow-up visit as compared to baseline. Statistically significant differences were observed for the overall population in the category of >80% when comparing compliance at baseline (51.4%) with that at the 3-month follow-up visit (84.7%).

SAFETY RESULTS:

A total of 261 patients (10%) experienced one or more adverse event (AE) of any grade. The most frequent AEs observed were weight gain (1.07% of all patients) and those affecting the nervous system as sedation (0.8%), somnolence (0.7%), extrapyramidal symptoms/parkinsonism (0.6%), akathisia/motor restlessness (0.57%) and other at lower rates. Two deaths occurred in the course of the study (one myocardial infarction; one suicide), classified as unrelated or doubtfully related to treatment received by the patient.

CONCLUSION:

The socio-demographic, clinical profile and adherence to various treatment strategies of schizophrenic patients were compared with those of patients presenting other mental disorders. Significant differences in compliance with pharmacological and non-pharmacological treatments were evident between patients with S and other mental diseases, as well as after some therapeutic strategy change are implemented.

Date of report: September 6th, 2007